

Bioavailability of Oral Pyridostigmine and Inhibition of Red
Blood Cell Acetylcholinesterase by Oral and Intravenous
Pyridostigmine

TASK ORDER #2

FINAL REPORT

David M. Kornhauser, M.D.
Brent G. Petty, M.D.
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19. ABSTRACT (continued)

The mean bioavailability of oral pyridostigmine syrup was 29.2%. Considerable interindividual variability was noted, with the range of bioavailability being 14.7% to 51.1%. The mean rate constant of absorption was 0.373/hr with a range of 0.149 to 1.441/hr. These absorption rate constants are equivalent to a mean absorption half-time of 1.06 hours with a range of 0.48 to 4.65 hours.

The pharmacokinetics of both oral and intravenous pyridostigmine have been defined using a two-compartment model. Considerable interindividual variability in elimination of pyridostigmine was found here as well. The mean total clearance was 779 ml/min with a range of 382 ml/min to 1511 ml/min, and the mean beta half-life was 0.8 hours with a range of 0.36 to 3.2 hours.

The subjects were monitored for toxicity with clinical laboratory tests of hematology and chemistry variables, electrocardiograms, vital signs, and coordination testing. All of the subjects tolerated pyridostigmine well, with no adverse symptoms. One subject developed a significant increase in serum creatine kinase and 2 subjects had trivial elevations in liver enzymes with no symptoms. No significant changes occurred in electrocardiograms, vital signs, coordination, or other clinical laboratory tests.

The relationship between pyridostigmine plasma levels and erythrocyte acetylcholinesterase inhibition was also defined. The erythrocyte acetylcholinesterase inhibition was delayed in both onset and dissipation compared to plasma pyridostigmine levels after both oral and intravenous pyridostigmine administration. The delay in effect was modelled by assuming the presence of an effect compartment and an E_{\max} concentration-effect relationship. According to this model, the mean rate constant of elimination from the effect compartment was 3.42/hr with a range of 1.22 to 5.76/hr. Thus, the mean half-time of drug effect at a constant plasma concentration was 0.20 hours (12 minutes) with a range of 0.12 to 0.57 hours. The mean plasma concentration of pyridostigmine required to produce 50% enzyme inhibition at steady state was estimated to be 29.5 ng/ml with a range of 17.3 to 41.1 ng/ml.

The time delay in enzyme inhibition could also be accounted for by a model which assumed that carbamylation of the acetylcholinesterase enzyme inactivated it and that hydrolysis of the inactivated enzyme restored activity. The mean estimate of the rate constant of inactivation was 0.087 ml/ng/hr with a range of 0.058 to 0.164 ml/ng/hr, while the mean estimate for the rate constant of reactivation was 2.736/hr with a range of 1.652 to 4.107/hr. These estimates are similar to estimates of the rates of the inactivation and reactivation of purified acetylcholinesterase previously measured in vitro by others.

Considerable intersubject variability in the drug's effect occurred after oral dosing. The peak erythrocyte acetylcholinesterase inhibition varied from 20 to 39% of the baseline enzyme activity, and the duration of at least 20% inhibition varied from 0.33 to 5.0 hours. The variation appeared to be due to interindividual differences in the amount of absorption of the drug, in the rate of elimination of the drug, and in the sensitivity of the acetylcholinesterase to inhibition by pyridostigmine.

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SUMMARY

Pyridostigmine bromide pretreatment has been shown to reduce the mortality from organophosphate exposure in animal studies. This human study was performed (1) to determine the bioavailability of oral pyridostigmine syrup, (2) to examine the pharmacokinetics and safety of pyridostigmine given orally and intravenously, and (3) to determine the relationship between pyridostigmine plasma levels and erythrocyte acetylcholinesterase inhibition after the oral and intravenous administration of pyridostigmine.

The first six subjects received oral and intravenous pyridostigmine (in a dose-ranging phase) in an effort to approach, but not exceed, 40% inhibition of erythrocyte acetylcholinesterase. This target level of inhibition was chosen as a compromise between effective protection against organophosphate poisoning on the one hand and toxicity from the drug on the other. After the proper doses to achieve approximately 40% erythrocyte acetylcholinesterase inhibition were determined, 18 additional subjects received oral and intravenous pyridostigmine to address the objectives mentioned above.

The mean bioavailability of oral pyridostigmine syrup was 29.2%. Considerable interindividual variability was noted, with the range of bioavailability being 14.7% to 51.1%. The mean rate constant of absorption was 0.373/hr with a range of 0.149 to 1.441/hr. These absorption rate constants are equivalent to a mean absorption half-time of 1.06 hours with a range of 0.48 to

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The time delay in enzyme inhibition could also be accounted for by a model which assumed that carbamylation of the acetylcholinesterase enzyme inactivated it and that hydrolysis of the inactivated enzyme restored activity. The mean estimate of the rate constant of inactivation was 0.087 ml/ng/hr with a range of 0.058 to 0.164 ml/ng/hr, while the mean estimate for the rate constant of reactivation was 2.736/hr with a range of 1.652 to 4.107/hr. These estimates are similar to estimates of the rates of the inactivation and reactivation of purified acetylcholinesterase previously measured in vitro by others.

Considerable intersubject variability in the drug's effect occurred after oral dosing. The peak erythrocyte acetylcholinesterase inhibition varied from 20 to 39% of the baseline enzyme activity, and the duration of at least 20% inhibition varied from 0.33 to 5.0 hours. The variation appeared to be due to interindividual differences in the amount of absorption of the drug, in the rate of elimination of the drug, and in the sensitivity of the acetylcholinesterase to inhibition by pyridostigmine.

FOREWORD

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

For the protection of human subjects, the investigators have adhered to the policies of applicable Federal Law 45 CFR 46.

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1. INTRODUCTION

Studies in animals have indicated that carbamate acetylcholinesterase inhibitors have protective effects against organophosphate poisoning. Pretreatment of animals with carbamates prior to nerve agent exposure has improved survival and effectively increased the LD₅₀ of nerve gas agents (1). Experimental carbamate pretreatment has been most effective when used in conjunction with atropine and oximes, both given following exposure (1,2). Of the carbamates studied, pyridostigmine has been found to be a useful agent with a duration of protective action of about two hours. The putative mechanism of action of carbamates is thought to be carbamylation of a fraction of the tissue acetylcholinesterase, thereby protecting the enzyme from irreversible inhibition by the organophosphate (3). The relatively rapid hydrolysis of the inactivated carbamylated enzyme has two sequelae. First, following a single dose of pyridostigmine, there is only a relatively short period of protection since pyridostigmine is rapidly removed from the body and the inactivated enzyme is rapidly reactivated by hydrolysis. Thus, if long term protection from possible organophosphate exposure is required, then repeated administration of pyridostigmine is required. Second (and on the positive side), if exposure to an organophosphate were to occur, the relatively short duration of action of pyridostigmine allows for reactivation of carbamylated acetylcholinesterase in a short

period of time, possibly minimizing the time period required for intensive therapy of the effects of cholinergic excess.

The dose of pyridostigmine and degree of acetylcholinesterase inhibition which provide adequate protection against organophosphate poisoning while at the same time remaining free of acceptable toxicity in man are not known. Studies in rats have indicated that inhibition of twenty-five percent of blood acetylcholinesterase does not affect muscle twitch tension, even after several days of therapy. On the other hand, abnormalities in twitch tension occurred in animals treated with enough pyridostigmine to produce sixty-eight percent inhibition of the enzyme (4). In addition, there are ultrastructural changes at the neuromuscular junction associated with this greater degree of inhibition of acetylcholinesterase (5). The changes appear to be dose related and, at least at low levels of enzyme inhibition, largely reversible.

The optimal use of pyridostigmine in man as prophylaxis for organophosphate poisoning thus presupposes that pyridostigmine is present in the body at the time of exposure and that a level of drug sufficient to provide protection while having few toxic effects can be achieved. With the fixed positive charge on the pyridostigmine molecule likely to make transdermal delivery difficult, multiple oral doses of drug appear to be, at least for the short term, the most feasible route of administration for prolonged protection. This study was designed to determine the amount of pyridostigmine required to produce modest levels of

erythrocyte acetylcholinesterase inhibition (approximately 40%) and to determine the bioavailability of oral pyridostigmine administered as the syrup that is currently commercially available. Once this fundamental information is obtained, the efficacy and systemic availability of other preparations can be evaluated and compared to the syrup as a standard.

2. MATERIALS AND METHODS

2.1 Pyridostigmine

Pyridostigmine was administered as the bromide salt. Mestinon^R, Roche Laboratory's brand of pyridostigmine bromide syrup, lot #0204, was provided by the U.S. Army for oral dosing. The oral doses were administered by expelling the syrup from a syringe directly onto the subject's tongue. The subject swallowed the dose immediately. Blood samples were obtained by means of an indwelling catheter in the arm which was kept patent by a dilute heparin solution. Organon brand pyridostigmine bromide, lot #485460A, was given intravenously to the first six subjects. A single lot, Roche lot #102, U.S. Army lot #BL10992, of injectable Mestinon was used for the intravenous infusions in subjects 07 through 24. Drug was diluted to 20 ml with normal saline and infused over 30 minutes with an infusion pump. Blood samples were drawn from an indwelling catheter in the contralateral arm. The volume of pyridostigmine administered was determined by weighing the syringe full of medication immediately

prior to dosing and subtracting the weight of the empty syringe after dosing, then dividing the difference by the specific gravity of the solution. Oral and intravenous dosing solutions were assayed for pyridostigmine concentration. The administered dose was then calculated from the product of the volume administered times the assayed concentrations (Appendix A).

2.2 Subjects

Healthy men who were able to give written informed consent were eligible to volunteer for the study. The study was approved by the Joint Committee on Clinical Investigation of The Johns Hopkins Medical Institutions and the Human Subjects Research Review Board of the U.S. Army.

2.2.1 Inclusion Criteria

To participate in the study the volunteer had to be male, between 18 and 35 years of age, and within 10% of his ideal body weight. A detailed health history and physical examination were performed by a physician. Serum chemistries, hematology and urine analysis had to be within normal ranges (except creatine kinase), as defined by The Johns Hopkins Hospital Department of Laboratory Medicine. The creatine kinase (CK) could be above the "normal range" and not exclude the subject because of the frequent finding of elevated CK in healthy subjects who are especially active physically (6-13). A chest x-ray within 6 months of entry and an electrocardiogram had to be

normal.

2.2.2 Exclusion Criteria

Women were excluded from this study. Men were excluded if they did not meet the criteria listed above (2.2.1) or if they had a known or suspected allergy to pyridostigmine or related drugs. Once accepted as candidates for the study, subjects were not permitted to take any medication for one week prior to admission to the study.

2.2.3 Recruitment

Advertisements were placed in the help wanted classified sections of metropolitan Baltimore newspapers. A special telephone line was dedicated to volunteer recruitment. Interested candidates were screened on the telephone by a research nurse who described the details of the study, took a brief history and scheduled the appropriate screening examinations.

2.2.4 Informed Consent

Written informed consent was obtained from each participant upon admission to the Clinical Research Unit. The consent document described in detail the purpose of the study, the research protocol, and the potential risks.

2.2.5 Compensation

A payment schedule was designed to compensate volunteers for their participation. Each volunteer was compensated as follows:

Screening phase	No compensation
In-hospital phase	\$375.00

Total per subject for entire study	\$375.00

For the entire study, \$9000.00 was distributed to 24 volunteers.

2.2.6 Liability

Liability coverage for unexpected toxicity was provided by the U.S. Army, and for malpractice by the Johns Hopkins Medical Institutions.

2.3 Experimental Protocol

2.3.1 Objectives

There were three objectives of the study. The primary objective was to determine the absolute bioavailability of pyridostigmine bromide when given as the oral syrup. However, since for safety reasons erythrocyte acetylcholinesterase inhibition could not exceed 40%, and because the assay of pyridostigmine base was possible only at concentrations greater than 1.5 ng/ml, it was first necessary to determine the oral and intravenous doses of pyridostigmine which would produce plasma

levels of drug high enough to measure but which inhibited the enzyme less than 40%. Once the appropriate doses were found, a formal bioavailability study with eighteen subjects was conducted. The other two objectives of the study were to examine the pharmacokinetics and safety of pyridostigmine given orally and intravenously, and to determine the relationship between pyridostigmine plasma levels and erythrocyte acetylcholinesterase inhibition after the oral and intravenous administration of pyridostigmine.

2.3.2 Design

The study was conducted as an open design study with each subject receiving both oral and intravenous pyridostigmine. Subjects were balanced insofar as the order of drug administration was concerned (i.e., first dose oral liquid or intravenous solution). The doses were spaced three days apart. The subjects were fasted and not allowed to smoke for 8 hours before each dose and for 4 hours after each dose, when they were allowed to eat and to smoke if they desired.

As mentioned above in 2.3.1, the study was conducted in two phases, an initial dose-ranging phase followed by a formal bioavailability phase. The outline of the study and the details of how it was to be conducted as initially planned are contained in the Procedural Timetable and Study Flow Charts (Appendix B). The first three subjects received 0.66 mg of pyridostigmine bromide intravenously and 20 mg orally. Assays of pyridostigmine

concentrations revealed barely detectable concentrations of drug after the IV infusion and inhibition of acetylcholinesterase was low. Therefore, the intravenous dose was doubled. Volunteers 04-06 received 1.32 mg of pyridostigmine bromide intravenously and 20 mg orally. Plasma concentrations after both routes of administration were measurable. However, inhibition of acetylcholinesterase after oral administration of 20 mg exceeded 40% at one time point in one volunteer. Accordingly, it was decided to decrease the oral dose for the formal bioavailability trial. In that second phase, eighteen subjects were given pyridostigmine bromide, 1.32 mg intravenously and 16 mg orally.

All subjects were screened outside the hospital. Drug administration, sampling and post-drug toxicology monitoring were performed in the Drug Development Unit of The Johns Hopkins Hospital.

2.4 Clinical Laboratory Examinations

All laboratory examinations except for assay of pyridostigmine were done within The Johns Hopkins Medical Institutions. Hematology and chemistry determinations were performed by the Department of Laboratory Medicine (Clinical Laboratory License number 19-1054). The normal values for these determinations are listed in Appendix C. Erythrocyte acetylcholinesterase assays were performed in the research laboratory of the Division of Clinical Pharmacology (see section 2.5.2).

2.4.1 Hematology

Routine hematologic determinations, including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count, reticulocyte count and platelet count, were done with a Coulter counter.

2.4.2 Chemistry

Serum was assayed for sodium, potassium, chloride, carbon dioxide, urea nitrogen, creatinine, glucose, uric acid, calcium, phosphate, total protein, albumin, cholesterol, direct and total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactic dehydrogenase and creatine kinase.

2.4.3 Electrocardiography

Standard 12-lead electrocardiographic tracings were taken on admission to the hospital and on days 3 and 6. Electrocardiograms were interpreted by a physician on the staff of The Johns Hopkins Hospital in the Division of Internal Medicine.

2.4.4 Urine Analysis

Urine analyses were performed in the laboratories of the Division of Clinical Pharmacology. Protein, ketones and bilirubin were measured qualitatively, and pH and specific gravity were determined. A microscopic examination of the

sediment was also performed.

2.4.5 Chest X-ray

Standard PA and lateral chest x-rays were usually taken just prior to admission to the hospital, and in all cases within 6 months of entry.

2.5 Pyridostigmine and Erythrocyte Acetylcholinesterase Determinations

2.5.1 Pyridostigmine Analysis

Blood samples for pyridostigmine assay were placed in heparinized Vacutainer^R tubes and iced immediately. As soon as possible (generally within five minutes) the samples were centrifuged in a refrigerated centrifuge. The plasma was separated and stored at -80° C until it was shipped in dry ice to the assay site.

The assay of pyridostigmine in plasma was performed under contract DAMD 17-85-D-0008, USAMRDC in the laboratory of Dr. Emil Lin at the School of Pharmacy, University of California at San Francisco (14). The assay utilizes protein precipitation with acetonitrile, pre-column purification on a small C8 Bond Elut^R column, and then high performance liquid chromatography on a silica column with ultraviolet detection. The detection limit is 1.5 ng pyridostigmine base/ml with a coefficient of variation between 3.55% and 8.16% (15). The plasma pyridostigmine concentrations of the patients in this study are listed elsewhere (15),

and are discussed below.

2.5.2 Erythrocyte Acetylcholinesterase Determinations

Blood for erythrocyte acetylcholinesterase determination was collected into Vacutainers^R containing ethylenediaminetetraacetic acid (EDTA), mixed immediately and brought to the Clinical Pharmacology laboratories for assay -- generally within five minutes of collection. Specimens were kept at ambient temperature until assayed. The assay was performed according to the Standard Operating Procedure (SOP) for the assay of the Analytical Chemistry Branch, USAMR, ICD, Aberdeen Proving Ground, Maryland 21010 dated 18 June 1985 (16). As performed at Johns Hopkins, the coefficient of variation of the assay determined from the quality control standard is 2.3%. Details of the assay and its performance at Johns Hopkins are contained in Appendix D.

2.6 Pharmacokinetic and Pharmacodynamic Analyses

2.6.1 Pharmacokinetic Analyses

Visual inspection of the pyridostigmine plasma concentration-time curves demonstrated that, following intravenous infusion, a biphasic decline in drug concentrations occurred. This suggested that the body can be represented by a two-compartment system. After oral administration, pyridostigmine concentrations rose gradually, followed by a short plateau and then a monophasic decline. In many subjects the data

were "noisy" both during the infusion and at low plasma concentrations. This "noise" made visual determination of the terminal elimination half-life difficult (and arbitrary) in many subjects. Estimates of the areas under the concentration-time curves by trapezoidal rule were also affected. Curve fitting of the intravenous data to the equation for a two-compartment model with a zero-order (constant infusion) input produced parameter estimates which varied markedly from patient to patient, suggesting that variability in the determination of the plasma concentrations was affecting adversely the curve fitting process. Since the shapes of the intravenous and oral concentration-time curves were consistent with a two-compartment open model with the rapid distribution phase being obscured by absorption during oral dosing, it was decided to fit the data after both intravenous and oral administration to a single model assuming a two-compartment open model with zero-order drug entry during infusion and with first-order absorption after a time lag following oral drug administration. This model assumes that the compartmental volumes and intercompartmental rate constants were the same during both experimental periods. Data from the oral and intravenous doses were used to fit simultaneously the equations for the time course of drug concentrations during the intravenous and oral administrations of pyridostigmine for seven constants: volume of the central compartment, K_{01} , K_{12} , K_{21} , K_{10} , time lag for absorption, and bioavailability. Data points were plotted on semilogarithmic paper. Points which appeared to be grossly

aberrant on visual inspection (far above or far beneath the two adjacent points) were not included in the curve fitting. The sample times which were excluded from the analysis are listed in Table 1. PCNONLIN^R, a commercially available curve fitting program for the IBM PC (17), was used to obtain the values for the constants which provided a best fit for the observed data. A weighted least squares approach was used to determine the best fit. Weights of the reciprocal of the calculated value of each point were used. In several subjects (08, 12, 14, and 22) peak pyridostigmine concentrations during the infusion did not correspond to the end of the reported infusion time. This discrepancy caused large residual errors in the curve fitting process. Accordingly, for these subjects, the duration of infusion used in the curve fitting program was set to the time at which the maximum concentration of drug appeared in the plasma. Once the microconstants were determined, the macroconstants were calculated. Alpha and beta elimination rate constants are thus the same for both the oral and intravenous dosing; only the coefficients vary. The equations and the relationships between the micro- and macroconstants are shown in Table 2.

2.6.2 Pharmacodynamic Modeling

The relationship between pyridostigmine concentrations and pyridostigmine effect (erythrocyte acetylcholinesterase inhibition) was analyzed in two different ways. In both analyses the analytical equations determined from the pharmaco-

kinetic modeling described above were used to represent the plasma concentrations of pyridostigmine after intravenous and oral administration. Inhibition of erythrocyte acetylcholinesterase measured at different times was used as data. Negative and zero values and 24-hour data points were excluded.

Plots of inhibition of erythrocyte acetylcholinesterase versus plasma pyridostigmine concentration produced counter-clockwise loops in all patients, suggesting that the drug effect is delayed relative to the concentration of drug. Accordingly, an "effect compartment analysis" as described by Sheiner and associates was performed (18-20). This type of analysis assumes that the delay in drug effect is due to the transfer of drug to a compartment where the drug acts, an "effect compartment." Negligible mass of drug is transported into this compartment so that the pharmacokinetic equations are not altered. The model assumes that drug enters the effect compartment from the central compartment at a rate K_{IE} and that drug leaves the effect compartment with a rate constant K_{EO} . Furthermore, it was assumed that pyridostigmine behaves as a standard competitive inhibitor of the erythrocyte acetylcholinesterase and that 100% inhibition of the enzyme is possible. Accordingly, inhibition of erythrocyte acetylcholinesterase is given by the concentration of pyridostigmine [Pyr] divided by the concentration of pyridostigmine plus the IC_{50} , where the IC_{50} is the concentration of pyridostigmine in the plasma which, at steady state, produces

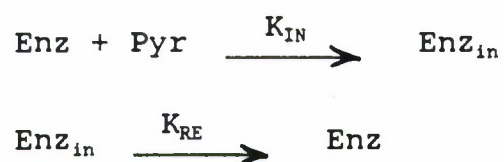
50% inhibition of enzyme activity.

$$\text{Inhibition} = \frac{[\text{Pyr}]}{[\text{Pyr}] + \text{IC}_{50}}$$

Initial analyses also included a Hill coefficient. However, when the data were fit to this model, there was a high correlation between the IC_{50} and the Hill coefficient, indicating insufficient information for an analysis with three parameters. The Hill coefficient varied around 1.0. Accordingly, it was fixed at 1 and a model including just the IC_{50} and the K_{EO} was employed. A schematic diagram of the model is depicted in Figure 1a. Inhibition data from both the oral and intravenous dosings were used simultaneously to obtain the best fit estimates of the 50% inhibition concentration of pyridostigmine and the rate constant of elimination from the effect compartment. The curve fitting program, PCNONLIN^R, was used with a weighted least squares regression analysis with weights being equal to the reciprocal of the calculated value of the inhibition.

Erythrocyte acetylcholinesterase inhibition was also related to the concentration of pyridostigmine in the plasma by using a biochemical model that has been used previously to study the in vitro inhibition of acetylcholinesterase (21). Acetylcholinesterase is inhibited by carbamylation of the enzyme. The inactivated enzyme is then reactivated by hydrolysis. The rate constant of inactivation is given by K_{IN} and the rate constant of reactivation is the constant K_{RE} . The differential equations for the two processes were written and solved for the fractional

inhibition of acetylcholinesterase.



PCNONLIN^R was used to fit the differential equation for the values of K_{IN} and K_{RE} which best described the data for each patient. Figure 1b depicts the schematic representation of this model. When inhibition data from the oral and intravenous dosings were used simultaneously to obtain a single value for each constant, the inhibition at late time points after oral inhibition was estimated poorly. Therefore, estimates of the rate constants were performed with the data from the oral dose and separately with the data from the intravenous dose. The estimates were averaged to produce a single estimate for the inactivation and reactivation rate constant for each subject. As before, weighted least squares estimates, with weights equal to the reciprocal of the calculated value, were obtained. The parameter estimates in Subjects 10 and 19, obtained using the inhibition data achieved after the oral dose, were markedly different from all other estimates. These two estimates have not been included in the summary statistics, having been eliminated as outliers.

2.7 Statistical Methods

Estimates of population parameters, the mean and standard deviation of the calculated variables, have been determined using standard formulae.

3. RESULTS AND DISCUSSION

3.1 Amendments and Compliance

3.1.1 Amendments

The consent form was amended prior to enrolling the first subject to provide information about toxicity in rats. The original consent form and the amended consent form are provided as Appendix E and F, respectively.

The protocol was amended after the first three subjects were completed to increase the intravenous dose of pyridostigmine bromide to 1.3 mg. The protocol was amended after subjects 04, 05, and 06 were completed to reduce the dose of oral pyridostigmine bromide to 16 mg. (Details are provided in section 2.3.2 of this document.) The protocol was amended to collect 24-hour urine specimens for pyridostigmine assay for the last 8 subjects. The institutional review board at Johns Hopkins and the Army's Human Subjects Research Review Board were notified of these changes and granted approval.

3.1.2 Compliance

After the completion of the study it was

discovered that the subjects had signed the originally approved consent form, not the amended version. The institutional review board at Johns Hopkins was notified of this oversight. No attempt was made to contact the subjects who had participated. We believe this had no bearing on the conduct of the study or on the willingness of our subjects to participate.

As mentioned in section 2.2.1, subjects were enrolled into the study even if screening and/or admission CK levels were elevated. We believe these elevations do not reflect a myopathic process, but rather reflect the extremely active physical lifestyle of the subjects. We are satisfied that these subjects were healthy and that those with elevated CK values did not have a pathological process.

Although we had requested and received approval to give 1.3 mg intravenous pyridostigmine bromide, we actually gave 1.32 mg. We believe this deviation is inconsequential.

There were six timed intervals for urine collection within each 24-hour period after dosing, not a single continuous 24-hour collection. This would allow for more precise information regarding urinary pyridostigmine excretion patterns. These data are included in the report prepared by Cheng et al. (22), and are discussed in the Results section (section 3.4.1) of this manuscript.

The baseline (pre-drug) electrocardiogram was done at screening and not on the day of admission to the hospital. This deviation is of no clinical importance.

Screening red blood cell acetylcholinesterase was not done before entry to the hospital. Rather, each subject's baseline red blood cell acetylcholinesterase level was determined before receiving the first dose of pyridostigmine and ascertained to be within the normal range.

Hand grip determination of muscle strength was not done after 09 January 1986 when the electronic device used for this purpose stopped working accurately. Values for this parameter are only complete for the first ten subjects. Neither the sponsor nor the institutional review board at Johns Hopkins was notified. There was no pattern of change in hand grip strength after pyridostigmine in the first ten subjects, and we believe this same pattern would have been similar for the remainder of the subjects. Furthermore, we believe that hand grip testing is a gross, and, in part, subjective measure of changes in voluntary muscle strength after pyridostigmine. It is subjective in that it is effort related and subject to the volunteer's interest and willingness to try hard.

The protocol divided the study into two phases: dose-ranging and bioavailability. The dose-ranging phase required 12 red blood cell acetylcholinesterase determinations for each dose, both intravenous and oral, while the bioavailability phase was designed to have 7 determinations for each dose. For all the intravenous doses, however, 12 samples were collected and assayed from all 24 subjects. No one was notified in advance of this protocol deviation, but we feel confident that these additional

samples were essential to allow the comprehensive pharmacokinetic and pharmacodynamic determinations included in this report. With regard to the oral dose, not only were the 12 sampling times intended just for the dose-ranging phase perpetuated into the bioavailability phase, but two additional sampling times were added, at 8 and 10 hours after the dose, when it became clear that acetylcholinesterase inhibition was still significant (approximately 10%) at 6 hours after the dose. Again, we believe that these additional data points were essential in enabling us to conduct the extensive analysis of pharmacodynamics outlined below.

3.2 Description of Population of Subjects

During the course of the study, a total of two newspaper advertisements were placed. Sixty-six men responded and, of this group, 24 were entered into the study. Reasons for rejecting potential subjects were:

66 Scheduled for screening

-24 Failed to keep scheduled appointment

42 Seen at Johns Hopkins Hospital

-12 Abnormal screening laboratory tests

- 4 Changed mind, moved, etc.

26 Examined by physician

-2 Failed history or physical exam

24 Admitted to Johns Hopkins Hospital and entered the study

24 Completed Study

Of the 24 who completed the study, 4 were white and 20 were black. The average age was 26.4 years and ranged from 19 to 35 years. Relevant vital statistics of the volunteers are listed in Table 3. Creatinine clearance was estimated from the Cockcroft-Gault formula (23) using the average of three in-hospital serum creatinine determinations for the serum creatinine concentration.

3.3 Clinical Results

3.3.1 Symptomatic

The subjects tolerated the administration of pyridostigmine very well and none complained of any side effect with either the intravenous or oral administration of the drug. In particular, there were no complaints of nausea, abdominal discomfort, change in bowel habits, muscle aching or tenderness, weakness, tremor, or any other neuromuscular complaint.

3.3.2 Pulse

No patterns of pulse change were consistently or predominantly seen in the subjects with administration of either intravenous or oral pyridostigmine. The pulse results appeared to be completely random and appeared to have no correlation with plasma pyridostigmine concentrations or with the degree of erythrocyte acetylcholinesterase inhibition.

3.3.3 Coordination Testing

There was no change in coordination testing compared to the baseline performance for any of the volunteers during or after administration of either intravenous or oral pyridostigmine. It should be noted that the coordination testing used was limited in its capacity to identify abnormalities. More refined and accurate methods of measuring coordination would need to be employed in order to identify subtle changes in coordination.

3.3.4 Hand Grip

As was the case with the pulse measurements, there was no recognizable or predominant pattern of change in hand grip for the subjects following administration of pyridostigmine. Not only was there little in common from one subject to the next, but there were also occasional discrepancies in the pattern of strength change over the period of observation in one hand compared to the other in the same subject. The hand grip testing was accomplished only for the first 10 subjects and was not done for the remainder because of technical difficulties with the hand grip measuring device.

3.3.5 Laboratory

3.3.5.1 Liver Function Tests

The serum aspartate aminotransferase (AST) levels increased in two subjects to a substantial degree

and above the upper level of normal (35 units/liter) after their second exposure to pyridostigmine, which in both cases was the intravenous dose. The levels increased from 20 to 44 units per liter in one subject and from 19 to 44 units per liter in the other. In only one of these subjects was the serum alanine aminotransferase (ALT) level found to increase as well, increasing from a predrug level of 12 to a level of 36 units per liter, 24 hours after the intravenous (second) dose. (The upper limit of normal is 30 units/liter). One other subject had a substantial increase in the serum alanine aminotransferase in the absence of a corresponding increase in the serum aspartate aminotransferase to an abnormal level. In this individual the ALT increased from 19 to 36 units per liter, again following the second exposure to pyridostigmine, which was the intravenous dose. No other subject had a noteworthy change in the serum transferases, and no subject had a significant change in alkaline phosphatase, serum cholesterol, total protein, serum albumin, direct or total bilirubin. The serum lactic dehydrogenase (LDH) increased modestly in one subject from a predrug level of 195 to a peak of 224 units per liter after the first (oral) dose of pyridostigmine and was back to normal 24 hours after the second (intravenous) dose of pyridostigmine, to a level of 170 units per liter. (The upper limit of normal is 200 units/liter.) The subject with the increase in LDH did not have an increase in either of the transferases. Thus, while the LDH may arise from the liver in some cases, it may originate from other organs and

there was no corroborative evidence suggesting that the liver was the source of this subject's minimal elevation.

3.3.5.2 Creatine Kinase

The creatine kinase was monitored in hopes of using it as a sensitive and fairly specific indicator of muscle cell damage. Interestingly, the creatine kinase level was well above normal in at least half of the subjects prior to receiving either formulation of pyridostigmine, and in most cases gradually fell over the course of the five day admission, consistent with muscle cell injury prior to admission to the hospital and gradual recovery over the course of the hospitalization. It is our impression that these elevations probably represent minor to modest degrees of muscle fiber damage as a result of strenuous exercise, physical exertion during gainful labor, or minor degrees of trauma suffered by our volunteers prior to admission. Only one subject had a remarkable increase in the creatine kinase. This individual had an increase from a level of 94 units per liter 24 hours after the first (oral) dose of pyridostigmine to a peak of 2,060 units per liter 24 hours after the second (intravenous) dose. As was mentioned above, neither this subject nor any others complained of symptoms suggestive of muscle injury, such as soreness, stiffness, or aching. Two other subjects had very modest elevations of creatine kinase following their second administration of pyridostigmine, in one case the administration being oral and in the

other case the administration being intravenous. In neither of these two subjects, however, was the increase nearly so impressive as that of the first subject described above. Therefore, we believe that the substantial elevation of creatine kinase in the one volunteer may be evidence for subclinical muscle injury in response to intravenous pyridostigmine, but the elevations seen in the other two subjects were clinically insignificant.

3.3.5.3 Other Clinical Chemistry Tests

No subject had an abnormality of any of the other monitored chemistry tests mentioned above under "Methods."

3.3.5.4 Hematological Testing

Three of the subjects had very mild reductions in their hemoglobin concentrations and hematocrits over the course of the study. The magnitude of these changes, however, was consistent with the phlebotomies being performed to obtain blood samples for monitoring and outcome measurements. No remarkable changes in white blood cell count occurred. Two subjects developed a very mild relative eosinophilia in the absence of symptoms or signs of hypersensitivity. There were no significant elevations of reticulocyte count over the course of the study.

3.3.5.5 Electrocardiograms

There were no significant changes in electrocardiograms following any dose of pyridostigmine. The only noteworthy changes were mild changes in electrical axis and non-specific ST-T wave changes, both of which might be due to expected intrasubject variability, though a drug effect cannot be excluded.

3.3.6 Clinical Conclusions

It is our view that the subjects tolerated the administration of pyridostigmine in both the oral and intravenous forms very well. The minimal elevations of transferases in 3 of the subjects were not clinically worrisome. The substantial elevation of creatine kinase in one subject is the only observation of clinical importance and could possibly be related to an increased propensity for muscle cell damage in response to intravenous pyridostigmine in this volunteer. Further evaluation of this observation, both in this subject and in others, would be warranted in our view. In our opinion, this single observation does not constitute grounds for any more specific action than to continue our close observation of this parameter.

3.4 Pharmacokinetics and Pharmacodynamics

3.4.1 Pharmacokinetics

Data from the 18 volunteers, 07-24, who received 1.32 mg of pyridostigmine bromide intravenously and 16 mg orally

were analyzed. The times the samples were obtained during and after the intravenous infusion are listed in Table 4. Measured plasma pyridostigmine base concentrations are found in Table 5. Plasma concentrations of pyridostigmine rose rapidly during the intravenous infusion and declined once the infusion had stopped. Plasma concentrations were no longer measurable six hours after beginning the infusion (Figure 2 and Tables 4 and 5).

Concentrations during and after the infusion were quite variable. Coefficients of variation at each sample time were greater than 25%. Peak concentrations at the end of the infusion varied as much as fourfold. During the phase of declining concentrations variations were somewhat less but still substantial. Individual plasma concentration curves are depicted in Figures 2a, 2c, and 2e.

Pyridostigmine concentrations following the dose of oral syrup rose slowly, often after a short time delay (Tables 6 and 7). The mean plasma concentrations were nearly constant from one to three and a half hours after dosing and then declined slowly over time. At ten hours after the dose pyridostigmine was still detectable in some subjects (Table 7 and Figures 2b, 2d, 2f). Variations between subjects were greater following oral dosing than following intravenous dosing (Figures 2a-2f). Coefficients of variation were greater than 32% at each time. In some subjects there was rapid absorption with a high peak concentration of pyridostigmine achieved and a relatively rapid decline (e.g., Subject 18) while in other subjects absorption was

delayed, the peak level was later and the decline slower (e.g., Subject 16).

The approach of fitting the oral and intravenous data simultaneously predicted the actual plasma concentration data using a two-compartment open model with different types of drug entry depending upon the route of administration. The sum of the weighted squared residuals and the correlations between the calculated and actual data points for each subject for both routes of administration are shown in Table 8. There was little difference between the means of the sum of the weighted squared residuals for the oral and intravenous routes of administration. Correlation coefficients were generally high, usually above 0.9. The correlation between the calculated and observed data for the intravenous route was higher than that for the oral route ($p < 0.002$, paired t-test). Several factors in the design and analysis of the trial may be responsible for this. First, more data points were collected during intravenous dosing than during the oral dosing and plasma concentrations tended to be higher, reducing the problems created by low measured values approaching the sensitivity of the assay. In this way the weighting procedure may have been biased toward the intravenous dosing. Second, an assumption was required to model the kinetics of the oral dose, i.e., first-order absorption of drug, which was not needed for the intravenous data. The absorption of pyridostigmine may, in fact, not follow strictly first-order kinetics, in which case the actual and estimated concentrations

would be expected to differ. For the intravenous dosing, the infusion was a constant one and modelled as such. In the few subjects where unusual concentration profiles occurred during the infusion, the model was modified (see 2.6.1). Finally, estimates of three parameters were obtained from the data following the oral dose in addition to the estimates derived from both the intravenous and oral data. The requirement of seven as opposed to four parameter estimates may have introduced a greater discrepancy between the actual and estimated plasma concentrations for the oral dosing.

The estimates of the pharmacokinetic microconstants for each subject are detailed in Table 9. Due to the simultaneous fit, there is only a single estimate for each of the microconstants. For each constant a wide variation between subjects exists, the standard deviation of the estimate being greater than 50% of the average estimate in all cases except for the bioavailability. The pharmacokinetic macroconstants, derived from the microconstants, are shown in Table 10. As in the case of the microconstants, there is great variation between subjects. The coefficient of variation is greater than 40% for each constant. The variability in the magnitude of these constants is reflected in the calculated areas under the concentration-time curves and the plasma clearances of pyridostigmine as well. The values for each subject are depicted in Table 11. Coefficients of variation of about 30% were present in the areas under the concentration-time curves following both intravenous and oral dosing. There

was a similar variation in the calculated total plasma clearances. Adjusting the total clearance for body weight or for renal function (estimated creatinine clearance) did not reduce the coefficient of variation.

The results of this study are similar to data collected by others who studied smaller numbers of subjects. Aquilonius et al. studied the intravenous kinetics of 2.5 mg of pyridostigmine bromide given to 2 subjects (24). Total clearance of drug was 806 and 828 ml per minute or 10.6 and 10.9 ml/min/kg. The plasma half-life of drug was 1.7 and 1.3 hours. Calvey and coworkers studied 10 patients after administering intravenously 3.65 mg of pyridostigmine bromide per 70 kg body weight (25). Clearance of drug in these patients averaged 16.3 ml/min/kg with a range of 9.3 to 26.5. Since the body weights of the individual subjects were not provided in their report, the values for the total clearances not normalized for weight cannot be calculated from the data. The beta half-life averaged 0.38 hours, ranging from 0.25 to 0.62 hours. The results of the current study (mean total clearance of 779 ml/min with a range of 382 to 1511 ml/min) are similar to the data above. When corrected for body weight, the present data yield a mean clearance of 10.3 ml/min/kg, a value similar to that obtained by the others. Likewise, our mean beta rate constant is 0.768 per hour which translates to a beta half-life of 0.90 hours, a value well within the range of the earlier data. As all these studies were performed with different doses of pyridostigmine, it appears likely that the clearance of

intravenous pyridostigmine is independent of dose.

The variance in the total clearance estimates among our subjects is not reduced by normalizing drug clearance for the estimated creatinine clearance, suggesting that total pyridostigmine clearance is either largely non-renal or that renal pyridostigmine excretion is not highly correlated with the glomerular filtration rate, at least in subjects with normal renal function. For subjects 17 through 24, urine was collected for 24 hours following dosing and assayed for pyridostigmine base using a modification of the assay for plasma (22). Amounts of pyridostigmine base excreted during each collection period are displayed in Table 12. Pyridostigmine was detectable in the urine within one hour after both intravenous and oral dosing. The amount of pyridostigmine excreted declined rapidly with time after intravenous dosing but persisted somewhat longer after oral dosing. The amounts of pyridostigmine excreted were variable among subjects, ranging from 33.8 to 84.9% of the intravenous dose and from 4.8 to 19.8% of the oral dose (Table 13). These urinary recoveries are similar in magnitude and variability to those found by Nowell et al. (26), who studied 5 patients with myasthenia gravis receiving 180 to 3600 mg of pyridostigmine bromide daily. Urinary excretion of intact pyridostigmine ranged from 2 to 16% of the dose with as much as 70% variation on different study days. Somani et al. recovered 9.4% of the pyridostigmine dose in the urine in the one patient they studied (27).

Renal clearances calculated using the fractional excretion of pyridostigmine after intravenous dosing times the total clearance are tabulated in Table 14. Renal clearance estimates range from 215 to 854 ml/min with a mean of 430 ml/min. All exceed the creatinine clearance of the subjects, implying renal secretion of pyridostigmine. The renal clearance estimates in this study are of similar magnitude to those obtained by Chan and Calvey (28) except for two high values of 854 and 694 ml/min. These clearance rates, approaching renal plasma flow, are unexplained. The magnitude of the clearance values is consistent with the hypothesis that pyridostigmine is secreted by the secretory system for organic bases which resides in the kidneys. This pathway is located in the proximal renal tubule and actively transports organic cations, including primary, secondary, tertiary and quaternary amines, in the direction of excretion (29). Renal clearance of such compounds can approximate renal plasma flow. Within the cationic system, however, there can be competition between compounds for excretion, including endogenous compounds, presumably mediated by competition for the putative carrier protein (29). The observation by Chan and Calvey that the renal secretion of pyridostigmine was reduced in two patients who were being treated concurrently with a basic drug (28) is also consistent with transport by the cationic transport system.

Little prior information exists on the bioavailability of oral pyridostigmine. Aquilonius et al. studied 2 patients to whom they administered 120 mg of pyridostigmine bromide in the

fasting state (24). The dosage form of the drug was not identified in their article. Pyridostigmine was 5.1 and 11.4 percent bioavailable in these subjects. Breyer-Pfaff et al. administered 60 mg of pyridostigmine bromide as a dragee 30 minutes after a standard meal (30). They found the drug to be 14.3% available with a range of 11.5 to 18.9 percent in the 10 patients studied. A much smaller dosage of drug, 16 mg, was to be used in the current study, and assay of the syrup plus determination of the weight of syrup administered revealed the actual dose to be an average of 14.8 mg (Appendix A). Bioavailability was much higher with this dose than the doses mentioned above, ranging from 14.7 to 51.1 percent with a mean of 29.2 percent. These data suggest that the fractional absorption of pyridostigmine decreases as the size of the dose is increased. However, the absolute amount of drug absorbed, calculated as the product of the dose administered times the bioavailability, does increase with increasing dose (with the caveat that different dosage forms and different conditions were present in each study). When the administered dose is calculated in milligrams of pyridostigmine base, the amount of drug given to volunteers in the three trials was 83.3, 41.6 and 10.3 mg, respectively. The average amount of drug absorbed was 6.8, 6.0 and 2.9 mg, respectively, with considerable scatter within each study. The data are depicted in Figure 3. Absorption, therefore, is not directly proportional to the dose. Even excluding the highest dosage, a fourfold dosage increment produced only a twofold increase in

absorbed drug. The curve may also bend (although data are limited) which hints at capacity-limited absorption of drug.

Systemic availability of pyridostigmine also can be estimated from the recovery of intact drug in the urine. Bioavailability calculated in this manner is listed in Table 14 and compared with the values obtained from the pharmacokinetic parameter estimation (Table 9). In general, the bioavailability calculated from the urinary data is lower (7 of 8 subjects), suggesting a systematic error. The cause of this is not certain. One possibility is that pyridostigmine decomposed in the urine during the collection process. This might be expected to be greatest in the 8-24 hour specimen. As shown in Table 12, urinary excretion after intravenous dosing was rapid, and nearly complete by the end of 8 hours, while urinary excretion after oral dosing showed greater amounts in the later collections compared to intravenous dosing. Thus, if there were decay of pyridostigmine in the urine during the 8-24 hour collection, the end result would be an underestimation of excretion predominantly after oral dosing, thus underestimating bioavailability.

The limited degree of absorption, the hint of capacity-limited absorption, and the positive charge on the pyridostigmine moiety all suggest that passive diffusion across the gastrointestinal membrane is not the mechanism for absorption of pyridostigmine. Solubilization of drug is unlikely to be a problem since pyridostigmine is a charged molecule which is very soluble in an aqueous environment. Two mechanisms, closely

related, which could account for both the variation in availability between subjects at the same dose and for the apparent saturation in absorption with increasing dose can be postulated. The first invokes a saturable transport mechanism, either active transport or facilitated diffusion. Variations in the capacity or affinity of the transport system for pyridostigmine could result in differences in availability. Second, there might be compounds within the gastrointestinal tract, possibly endogenous, which are transported by the same system. These compounds might then compete with pyridostigmine for uptake; differences in the amounts of competing compounds from subject to subject would produce the variation in availability. Since all bioavailability studies were conducted with the subjects fasted at least 8 hours, food was not a factor in this study.

The small rate constant of absorption (mean equal to 0.373/hr) which is equivalent to a half-time of absorption of 1.86 hours, is also consistent with a capacity-limited transport process. Again, drug solubility is not likely to be an issue. Given in solution, pyridostigmine should be accessible to membranes almost immediately. Arrival at the absorption site and crossing the membrane must be the rate limiting steps. The time lag for absorption to begin, averaging over twenty minutes, represents the time required to arrive at the membrane transfer site, and variations in gastrointestinal motility might be responsible for the large differences observed in the time necessary to initiate absorption. Alternatively, the transport

hypotheses postulated earlier could account for some of the observed differences in the delay of absorption.

3.4.2 Pharmacodynamics

Following pyridostigmine administration inhibition of erythrocyte acetylcholinesterase occurred. Inhibition increased rapidly during the intravenous infusion, reaching a mean of 30% at the end of the 30-minute infusion (Table 15). Enzyme inhibition declined thereafter, and six hours after dosing the enzyme activity had returned to baseline. The degree of inhibition at the end of the infusion varied almost twofold, from 22% to 39%. Later, more than one and a half hours after the onset of the infusion, inhibition varied by as much as threefold, though the absolute differences between subjects were less, no more than 11%. The mean inhibition as a function of time is shown in Figure 4, with data of individual patients depicted in Figures 4a, 4c, and 4e.

Inhibition of erythrocyte acetylcholinesterase following oral pyridostigmine developed less rapidly (Table 16 and Figure 4). There was a gradual rise in mean inhibition with the peak occurring at three hours after dosing. Inhibition was nearly constant, however, from 1.3 to 4.0 hours. Thereafter, the proportion of enzyme inhibited declined so that 10 hours after dosing the mean inhibition was only 6%. At 24 hours, the next sample time, no inhibition was measured. Variations from subject to subject in the amount of inhibition achieved were greater

during the oral dosing than during the intravenous dosing (Figures 4b, 4d and 4f and Tables 15 and 16). Differences between maximum and minimum amounts of inhibition at each sample time ranged from 10 to 20%. At times later than 4 hours after the oral dose, some subjects had three to four times as much enzyme inhibition as others. Ten hours after dosing, inhibition ranged from 2 to 11% of baseline enzyme activity.

Inhibition of erythrocyte acetylcholinesterase above 20% was more effectively prolonged after oral dosing than after intravenous administration. During the intravenous dose at least 20% inhibition was reached in all subjects. After the infusion was completed, however, the degree of inhibition fell rapidly. By 1.17 hours after the end of the infusion, inhibition was less than 20% in all subjects (Table 15). The mean duration of inhibition greater than 20% was only 0.49 hours (Table 17). The longest duration, observed in Subject 12, was only 1.08 hours. In contrast, after the oral dose, inhibition of erythrocyte acetylcholinesterase remained greater than 20% for an average of 2.62 hours (Table 18). Variability of inhibition was greater with oral than with intravenous administration. After oral dosing, inhibition over 20% was present at only one measurement in Subject 9 (Table 16), while inhibition greater than 20% was present for 5 hours in Subject 14 (Table 18). The maximal inhibition of erythrocyte acetylcholinesterase in each subject for each dosage form is provided in Tables 19 and 20. The mean time to peak inhibition was 2.5 hours after oral dosing (Table

20), while in all cases but one (Subject 9) the peak inhibition with intravenous dosing was seen at 0.5 hours, corresponding to the end of the infusion (Table 15).

For both the intravenous and oral dosing, the fraction of red blood cell acetylcholinesterase inhibition was plotted against the concentration of pyridostigmine in the plasma (Figure 5a and 5b). When the data points were connected in order of time after dosing, an anticlockwise loop was obtained. A loop in this direction suggests that the effect of the drug is delayed relative to the plasma concentration of the drug. The area within the hysteresis loop for both doses for each patient was calculated. The mean area in the loop following the intravenous dose and the mean area in the loop following the oral dose were each significantly greater than zero. In addition, the area of the loop during the intravenous dose was greater than that from the oral dose. Data of individual subjects are detailed in Table 21.

Since the above plots suggested a delay in the effect of the drug, we employed an effect compartment model to explain the delay. The pharmacokinetic equations previously described were used to estimate pyridostigmine in the effect compartment. Using the oral and intravenous inhibition data simultaneously, we sought the K_{E0} and the IC_{50} concentration of pyridostigmine which best described the data.

The ability to fit the data to this model was quite good (Table 22). Correlations between the predicted inhibition and

observed inhibition were above 0.8 in all instances and in the majority of cases above 0.9. The estimates had slightly higher correlations with the intravenous data than the oral data but the difference was not significant. The sum of the weighted squared residuals was small in all instances of fitting the intravenous data and in most instances for fitting the oral data. The estimate was particularly high for the oral dosing of patient 10 for reasons not apparent. Curve fittings of the oral data were not as good as those for the intravenous data. This may be due in part to the fact that the equations for the pyridostigmine concentrations did not describe the actual oral data as well as they did the intravenous data.

The mean K_{EO} , or rate constant of elimination from the effect compartment, was 3.42 per hour, equivalent to a half-time at steady state in the effect compartment of 0.2 hours (Table 23). There was a greater than fourfold variation in the magnitude of the estimates of this constant, from 1.22 to 5.76 per hour. These rate constants are equivalent to a half-time of effect of 0.57 and 0.12 hours, respectively. The concentration of pyridostigmine in the plasma which would produce 50% inhibition of effect at steady state, the IC_{50} , also varied. The mean of the estimates was 29.5 ng/ml. Individual estimates, however, ranged from 17.3 to 41.1 ng/ml, a 2.5-fold difference.

This analysis suggests that there are significant interindividual differences in the sensitivity of erythrocyte acetylcholinesterase to pyridostigmine. These differences are

manifest both in the time it would take, at a constant pyridostigmine concentration, to achieve steady state inhibition of enzyme and also in the amount of pyridostigmine required in the plasma to produce a given amount of inhibition of the erythrocyte acetylcholinesterase. In the first instance, since three to five half-lives are required to reach steady state, one would expect that it would take from 20 minutes to 2.5 hours to achieve steady state inhibition of enzyme, depending on the rate constant of elimination (K_{E0}) from the effect compartment. Regarding the IC_{50} variability, if the pharmacokinetic parameters were identical in a group of subjects, some subjects would still require 2.5 times as much drug to produce a given effect as others. Those with low IC_{50} 's would be sensitive to the drug and would require lower doses, while those with elevated IC_{50} 's would require larger amounts of drug.

The effect compartment analysis, while useful, is not a completely accurate representation of the interaction between pyridostigmine and the erythrocyte acetylcholinesterase. The interaction is not really reversible, at least in the classical sense of almost instantaneous association and dissociation of enzyme with inhibitor. After carbamylation the hydrolysis, equivalent to dissociation, is delayed. Furthermore, since the red blood cell is circulating in the plasma, the interaction between drug and enzyme should occur in the central, highly perfused, kinetic compartment. Given these conditions, it seemed reasonable to model the interaction between enzyme and drug

producing enzyme inhibition using available information about the biochemistry of the enzyme. It was assumed that separate rate constants describe the inactivation of enzyme by pyridostigmine and the reactivation of inactivated enzyme by hydrolysis. These two constants were denoted K inactivation (K_{IN}) and K reactivation (K_{RE}), respectively. Attempts at fitting the observed inhibition data to the model using the data from both the intravenous and oral doses simultaneously were unsuccessful; the inhibition which occurred at late time points following oral dosing could not be accurately estimated. However, when separate estimates were produced from the oral dosing and from the intravenous dosing, reasonable estimations of acetylcholinesterase inhibition could be produced. As in the case of the effect model, estimates of the effect following the intravenous dose were marginally better than the estimates for the effects after the oral dose. Sums of the weighted squared residuals were small for both routes of administrations and in all patients. Correlation coefficients for the relationship between the observed and predicted inhibition were greater than 0.9 in all cases but one. Correlation coefficients were higher for the estimates of the intravenous effects than for the oral ($p < 0.02$ by paired t-test). The data for the "goodness of fit" to this model for each subject are detailed in Table 24.

Two estimates of each biochemical rate constant, one from the intravenous dosing and one from the oral dosing, were obtained for every subject and averaged (Table 25). The two estimates for

each constant in each patient were generally similar. Nevertheless, the estimates in two subjects (10 and 19) using the data obtained after oral administration of drug were clearly at variance with the 34 other estimates. The reasons for this are not apparent. Subject 10 had unusual pharmacokinetics with a much greater plasma clearance of pyridostigmine than the other volunteers. The parameter estimate for K_{IN} generated from Subject 10's intravenous data is the largest estimate from the intravenous data, but the estimate for K_{RE} is not substantially different from those generated in the other subjects. The estimate of the constants in Subject 19 from the data following intravenous dosing of pyridostigmine and the pharmacokinetics of pyridostigmine appear similar to the estimates in the other subjects. The two aberrant results have been excluded from the computation of the estimates of the mean and standard deviation of K_{IN} and K_{RE} . Whether the two unusual values are a consequence of the curve fitting process and thereby artifactual, or whether they represent some unusual occurrence during the oral dosing of these two subjects, is not known.

Excluding the aberrant results of Subjects 10 and 19 as described above, there was a coefficient of variation of 25 to 33% in the estimates of the biochemical rate constants. The mean inactivation rate constant was 0.087 ml/ng/hr and the mean reactivation rate constant was 2.736/hr. The latter represents the rate at which inactive enzyme is reactivated. This mean rate constant is equivalent to a half-time of reactivation of 0.25

hours, indicating that, on the average, it would take three to five half lives, or 0.75-1.25 hours, for inactivated enzyme to be completely reactivated, even in the absence of pyridostigmine. The smallest reactivation rate constant was 1.65/hour. In this subject it would take up to two hours to completely reactivate the enzyme. The heterogeneity in these two rate constants is similar in magnitude to the variation in the magnitude of the effect compartment elimination rate constant and the IC_{50} determined in the preceding analyses.

The values for the two estimated constants can be expressed in the units used to describe biochemical reaction rate constants. These are, in the case of K inactivation, liters per mole per minute, and in the case of the reactivation rate constant, per minute. The estimate of the inactivation rate constant of pyridostigmine for acetylcholinesterase in intact erythrocytes is thus $26.3 \pm 8.2 \times 10^4$ L/mole/min. This compares quite favorably to an estimate of 19.8×10^4 L/mole/min for k_1 , the reaction rate of pyridostigmine with purified bovine erythrocyte acetylcholinesterase in vitro at 37°C measured by Watts and Wilkinson in 1977 (21), and an estimate of 1.6×10^4 L/mole/min for the inactivation rate of electric eel acetylcholinesterase performed in vitro by Wilson et al. (31). The latter experiments were performed at 25 degrees Celsius; the reaction rate would be expected to be higher at body temperature (37°C), in part explaining the tenfold difference. The mean estimate obtained in the present study for the rate of enzyme reactivation (hydrolysis

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restored immediately after drug is removed. Rather, enzyme inhibition is gradually dissipated as the carbamylated, inhibited enzyme is reactivated by hydrolysis. The intersubject variations in the estimates for the rate constants may represent true differences in the interactions between the drug and the enzyme, possibly related to molecular heterogeneity of the enzyme. Another possibility is that these differences are artifacts of the experimental, analytical, and mathematical processes which were required to obtain the estimates. Small errors generated in each of these processes might have contributed sufficiently in the aggregate to produce the scatter in the estimates.

4. CONCLUSIONS

Analysis of the experimental data from this study indicates that significant interindividual variation in erythrocyte acetylcholinesterase inhibition will result from a uniform dose of pyridostigmine. This interindividual variation in drug effect is a consequence of two major factors: (1) the variation in the pharmacokinetic parameters in any group of individuals, and (2) the variability of the concentration-inhibition relationship (pharmacodynamics) between pyridostigmine and acetylcholinesterase in different subjects.

Pharmacokinetic variations appear to be at two major sites. The first major factor in the variability of pyridostigmine pharmacokinetics is in the bioavailability of the oral

formulation of the drug. There were large differences in both the extent and rate of absorption of pyridostigmine in the volunteers in this trial. The amount of drug absorbed from the liquid preparation given varied fourfold within these 18 subjects. This is presumably a situation where the pharmaceuticals are optimal for drug absorption, i.e., a freely soluble drug administered in solution. Other workers using different doses and different dosage forms have also seen significant variation in the extent of pyridostigmine absorption. Differences in the time of onset of absorption were also observed. Nevertheless, while these might be fairly significant for single dose administration, for chronic dosing the time lag for absorption would not be a major factor in the systemic availability of pyridostigmine. Second, there are large differences in the plasma clearance of pyridostigmine between healthy volunteers. These differences cannot be explained on the basis of the estimated glomerular filtration rates of these individuals, even though the drug is apparently excreted primarily by the kidney. This suggests that some other variable (as yet unidentified) is a major determinant of pyridostigmine elimination. The large differences in the amount of drug entering the systemic circulation and in the variability in the rate at which drug leaves the systemic circulation would therefore be expected to result in large individual differences in the steady state plasma concentrations of pyridostigmine with any standard dosage regimen if it were applied to a large population.

The analyses of the concentration-inhibition (pharmacodynamic) relationship between pyridostigmine and erythrocyte acetylcholinesterase from this study also indicate that there is significant interindividual variation in enzyme inhibition at any given concentration of pyridostigmine. Both analyses performed, i.e., the effect compartment model and the biochemical model, suggest that within the small number of subjects studied there is a twofold difference in the sensitivity of erythrocyte acetylcholinesterase to pyridostigmine. Thus, even if a dosage form and dosage regimen could be devised to achieve a target pyridostigmine concentration in the plasma, there would be nearly a twofold difference in the amount of erythrocyte acetylcholinesterase inhibition in the population because of differences in the sensitivity of the enzyme to the drug. To the extent that the red cell enzyme is a marker for acetylcholinesterase at other sites, protection against organophosphate poisoning would also be expected to be highly variable. Therefore, a strategy to provide optimum protection against organophosphate poisoning may require individualized dosage regimens using the effect of the drug as the end point.

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Table 1

Sample Times with Measured Plasma Concentrations
Below the Minimum Detectable Level Which were
Not Included as Data Points for the Pharmacokinetic
Curve Fitting¹

Subject	IV Dosing	PO Dosing
8	2.0	
9	0.33, 0.917	
11	0.167, 0.25	
12		3.0
13	0.417	5.0
14	0.33	10.0
16	2.5	2.0, 3.5
17	0.167	
19	0.417, 2.5	0.5, 6.0
	3.0, 3.5, 4.0	
21	0.83, 1.33	
22		7.0
23	0.083, 0.417	
	2.0	
24	2.5	

¹All sample times are in hours after dosing.

Table 2

Equations To Which the Plasma Pyridostigmine
Concentrations Were Fit

Constants:

IVD intravenous dose
OD oral dose
TI duration of intravenous infusion

Parameters to be estimated:

V volume of the central compartment
K10 rate constant from central compartment to outside
K12 rate constant from central to peripheral compartment
K21 rate constant from peripheral to central compartment
K01 absorption rate constant, from outside to central
compartment
AVA availability of oral dose
TL time lag for absorption to begin

C(T) is the concentration of pyridostigmine at time T

For the intravenous dose:

$$C(T) = A(e^{-\alpha T} - e^{-\alpha T_s}) + B(e^{-\beta T} - e^{-\beta T_s})$$

where

$$\begin{aligned} T_s &= T - TI & \text{for } T > TI \text{ and} \\ T_s &= 0 & \text{for } T < \text{or } = TI \end{aligned}$$

$$A = (IVD/TI) * (K21 - \alpha) / V / (\alpha - \beta) / \alpha$$

$$B = -(IVD/TI) * (K21 - \beta) / V / (\alpha - \beta) / \beta$$

α and β ($\alpha > \beta$) are the positive and negative
roots of the quadratic:

$$r^2 + (K12 + K21 + K10)r + K21 * K10 = 0$$

For the oral dose:

$$C(T) = A e^{-\alpha T_o} + B e^{-\beta T_o} + C e^{-K01 T_o}$$

where

$$\begin{aligned} T_o &= T - TL & \text{for } T > TL \text{ and} \\ T_o &= 0 & \text{for } T < \text{or } = TL \end{aligned}$$

$$A = (AVA * OD / V) * K01 * (K21 - \alpha) / (\alpha - \beta) / (\alpha - K01)$$

$$B = -1 * (AVA * OD / V) * K01 * (K21 - \beta) / (\alpha - \beta) / (\beta - K01)$$

$$C = (AVA * OD / V) * K01 * (K21 - K01) / (\beta - K01) / (\alpha - K01)$$

α and β ($\alpha > \beta$) are the positive and negative
roots of the same quadratic as used for the intravenous dose

Table 3

Vital Statistics of Subjects Receiving Pyridostigmine

SUB #	WT kg	SCr* mg/ml	AGE yr	EST CL _{Cr} ** ml/min
1	65.7	.97	35	92.94
2	64.4	1.13	25	116.23
3	89.9	.87	27	122.75
4	63.5	1.00	25	101.42
5	60.3	.93	22	91.91
6	52.2	.90	26	74.39
7	80.5	.97	28	121.47
8	75.9	.97	35	107.37
9	76.5	1.30	30	151.94
10	77.0	.97	31	113.07
11	77.1	1.23	28	147.52
12	79.2	1.15	29	140.41
13	62.7	.97	30	92.92
14	86.5	.97	24	135.18
15	79.2	1.10	21	143.99
16	104.8	1.00	27	164.48
17	65.0	1.03	22	109.72
18	78.8	.97	22	125.27
19	61.6	1.10	22	111.05
20	76.2	1.13	24	138.73
21	72.3	1.10	19	133.65
22	70.1	1.03	24	116.33
23	83.0	1.05	20	145.25
24	68.0	.95	32	96.90
AVG 07-24	76.36	1.05	26.00	127.51
STD DEV 07-24	9.87	.10	4.61	20.06

* SCr = serum creatinine

** Calculated from the equation of Cockcroft and Gault

$$Cl_{Cr} = ((140 - \text{age}) * (\text{wt in kg})) / 72 * SCr$$

Table 4

Sampling times During and Following Intravenous Pyridostigmine

SUBJ#	SCHEDULED TIME OF SAMPLE													
	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
SUBJ#	ACTUAL TIME OF SAMPLE (HRS)													
	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
7	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
8	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.867	1.000	1.333
9	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.600	0.667	0.750	0.833	0.917	1.000	1.333
10	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
11	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
12	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
13	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
14	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.887	0.750	0.833	0.917	1.000	1.333
15	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.867	0.750	0.833	0.917	1.000	1.333
16	0.000	0.083	0.167	0.250	0.333	0.417	0.483	0.583	0.667	0.750	0.833	0.917	1.000	1.333
17	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
18	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
19	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
20	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
21	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
22	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
23	0.000	0.083	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
24	0.000	0.150	0.167	0.250	0.333	0.417	0.500	0.583	0.667	0.750	0.833	0.917	1.000	1.333
#	18	18	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.000	0.087	0.167	0.250	0.333	0.417	0.499	0.584	0.667	0.750	0.833	0.914	1.000	1.333
SD	0.000	0.016	0.000	0.000	0.000	0.000	0.004	0.004	0.000	0.000	0.000	0.012	0.000	0.000
CV(%)	0.000	18.210	0.000	0.000	0.000	0.000	0.803	0.686	0.000	0.000	0.000	1.289	0.000	0.000
MAX	0.000	0.150	0.167	0.250	0.333	0.417	0.500	0.600	0.667	0.750	0.833	0.917	1.000	1.333
MIN	0.000	0.083	0.167	0.250	0.333	0.417	0.483	0.583	0.667	0.750	0.833	0.867	1.000	1.333

SUBJ#	SCHEDULED TIME OF SAMPLE													
	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
	ACTUAL TIME OF SAMPLE (HRS)													
7	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
8	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
9	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
10	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
11	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
12	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
13	1.667	2.000	2.500	3.000	3.500	4.000	5.000	5.967	7.000	8.000	10.000	12.000	24.000	
14	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
15	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
16	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
17	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
18	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
19	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	23.883	
20	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	23.950	
21	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
22	1.667	2.000	2.500	3.000	3.500	4.000	5.000	8.000	7.000	8.000	10.000	12.000	24.000	
23	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
24	1.667	2.000	2.500	3.000	3.500	4.000	5.000	8.000	7.000	8.000	10.000	12.000	24.000	
#	18	18	18	18	18	18	18	18	18	18	18	18	18	
MEAN	1.667	2.000	2.500	3.000	3.500	4.000	5.000	5.998	7.000	8.000	10.000	12.000	23.991	
SD	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.008	0.000	0.000	0.000	0.000	0.029	
CV(%)	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.130	0.000	0.000	0.000	0.000	0.122	
MAX	1.667	2.000	2.500	3.000	3.500	4.000	5.000	6.000	7.000	8.000	10.000	12.000	24.000	
MIN	1.667	2.000	2.500	3.000	3.500	4.000	5.000	5.967	7.000	8.000	10.000	12.000	23.883	

Table 5

Concentration of Pyridostigmine During and Following Intravenous Pyridostigmine^{1,2}

SUBJ#	SCHEDULED TIME OF SAMPLE													
	0.00	0.08	0.17	0.25	0.33	0.42	0.50	0.58	0.67	0.75	0.83	0.92	1.00	1.33
	PYRIDOSTIGMINE CONCENTRATION ng/ml													
7	0.00	8.51	13.80	18.40	15.60	16.30	17.90	13.00	10.10	9.95	7.65	6.16	6.34	4.14
8	0.00	9.69	20.90	18.90	14.50	13.50	11.70	10.80	8.15	5.82	5.26	4.34*	3.51	3.37
9	0.00	4.75	8.73	13.60	25.90	18.30	20.30	14.00*	9.24	9.19	6.29	2.63	6.27	4.04
10	0.00	2.27	5.23	3.94	6.06	9.81	12.40	7.46	5.32	4.78	3.68	2.99	2.81	1.62
11	0.00	5.11		3.37	19.20	23.30	27.80	25.70	19.50	13.90	12.70	9.38	8.65	6.10
12	0.00	3.37	10.40	20.30	30.90	28.10	22.10	16.30	12.80	17.30	8.30	8.30	9.06	6.17
13	0.00	8.78	11.70	25.00	32.50	19.70	46.80	15.20	14.10	11.20	8.34	6.12	7.06	2.50
14	0.00	11.60	17.70	23.10	19.00	33.30	24.50	20.20	11.30	6.59	6.70	4.07	4.42	3.04
15	0.00	8.11	13.90	18.20	16.40	14.00	18.00	12.50	8.67	8.96	5.37	3.86	5.30	2.25
16	0.00	7.83	10.90	14.20	14.60	19.40	21.00*	11.00	8.64	10.70	7.20	5.83	5.85	2.63
17	0.00	8.87	6.17	12.90	14.20	16.20	20.70	10.10	8.92	6.16	5.22	3.82	3.10	2.29
18	0.00	6.90	10.50	12.30	12.90	20.60	18.90	14.50	10.50	5.67	5.50	4.61	4.37	3.19
19	0.00	10.80	17.10	17.50	18.60	14.20	24.20	17.60	10.10	8.42	6.93	6.80	7.12	5.07
20	0.00	9.09	12.60	20.50	19.90	26.80	29.50	18.10	16.80	10.30	6.98	6.26	5.18	5.79
21	0.00	19.60	16.30	20.70	21.70	19.00	22.70	13.70	10.50	7.54	7.02	5.66	3.86	5.84
22	0.00	7.80	14.90	22.40	21.80	24.80	20.60	11.60	11.30	8.55	6.59	4.80	6.36	4.09
23	0.00	12.30	8.39	16.70	22.60	14.90	20.50	12.70	11.00	14.80	9.26	7.74	3.86	4.24
24	0.00	9.91*	11.20	13.00	19.20	22.30	20.80	17.00	12.40	9.04	6.98	6.77	5.37	3.19
#	18	18	17	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.00	8.63	12.38	16.39	19.20	19.68	22.24	14.53	11.07	9.38	7.00	5.56	5.47	3.86
SD	0.00	3.84	4.18	5.93	6.35	5.96	7.54	4.23	3.27	3.34	1.95	1.84	1.79	1.44
CV(%)	0.00	44.50	33.78	36.20	33.08	30.30	33.91	29.12	29.52	35.62	27.82	33.03	32.79	37.14
MAX	0.00	19.60	20.90	25.00	32.50	33.30	46.80	25.70	19.50	17.30	12.70	9.38	9.06	6.17
MIN	0.00	2.27	5.23	3.37	6.06	9.61	11.70	7.46	5.32	4.78	3.68	2.63	2.81	1.62

	SCHEDULED TIME OF SAMPLE												
SUBJ#	1.67	2.00	2.50	3.00	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
	PYRIDOSTIGMINE CONCENTRATION ng/ml												
7	2.86	2.58	2.71	1.95	2.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
8	2.75	0.00	1.59	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
9	1.81	2.38	2.21	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
11	6.07	4.07	3.31	3.86	3.23	2.70	2.01	0.00	0.00	0.00	0.00	0.00	0.00
12	4.66	3.31	2.53	1.74	1.57	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
13	2.34	0.00	0.00	0.00	0.00	0.00	0.00	0.00*	0.00	0.00	0.00	0.00	0.00
14	2.92	2.04	1.62	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15	1.97	2.63	1.83	2.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
16	1.67	0.00	2.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
17	1.71	0.00	0.00	0.00	0.00		0.00	0.00	0.00	0.00	0.00	0.00	0.00
18	2.34	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
19	3.16	1.81	8.59	3.66	3.71	1.54	0.00	0.00	0.00	0.00	0.00		0.00*
20	3.99	3.87	1.70	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00*
21	2.41	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
22	3.66	1.75	2.76	1.73	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
23	3.80	0.00	2.92	0.00	0.00	0.00					0.00	0.00	0.00
24	3.77	4.40	4.64	1.57	1.93	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
#	18	18	18	18	18	17	17	17	17	17	18	17	17
MEAN	2.88	1.60	2.03	0.92	0.70	0.25	0.12	0.00	0.00	0.00	0.00	0.00	0.00
SD	1.35	1.63	1.76	1.32	1.24	0.73	0.49	0.00	0.00	0.00	0.00	0.00	0.00
CV(%)	46.71	101.98	86.70	143.25	177.50	294.02	412.31	0.00	0.00	0.00	0.00	0.00	0.00
MAX	6.07	4.40	6.59	3.86	3.71	2.70	2.01	0.00	0.00	0.00	0.00	0.00	0.00
MIN	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

*

Sample was not obtained at the scheduled time. See Table 4 for the time of sample.

1

Concentrations are nanograms of pyridostigmine base/ml

2

Concentrations less than 1.5 ng/ml, the lower limit of detectability of the assay are denoted 0.00

Table 6

Sampling Times Following Oral Pyridostigmine

SUBJ#	SCHEDULED TIME OF SAMPLE									
	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
	ACTUAL TIME OF SAMPLE (HRS)									
7	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
8	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
9	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
10	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
11	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
12	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
13	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
14	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
15	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
16	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
17	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
18	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
19	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
20	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
21	0.00	0.25	0.50	0.73	1.00	1.33	1.67	2.00	2.50	3.00
22	0.00	0.28	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
23	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
24	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
#	18	18	18	18	18	18	18	18	18	18
MEAN	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
SD	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CV(%)	0.00	3.09	0.00	0.53	0.00	0.00	0.00	0.00	0.00	0.00
MAX	0.00	0.28	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
MIN	0.00	0.25	0.50	0.73	1.00	1.33	1.67	2.00	2.50	3.00

SUBJ#	SCHEDULED TIME OF SAMPLE								
	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
ACTUAL TIME OF SAMPLE (HRS)									
7	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
8	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
9	3.50	4.00	5.00	6.00	7.13	8.00	10.00	12.00	24.00
10	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.37
11	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
12	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
13	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
14	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
15	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
16	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
17	3.58	4.00	5.17	6.00	7.00	8.00	10.00	12.00	24.00
18	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
19	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
20	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
21	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
22	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
23	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
24	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00
#	18	18	18	18	18	18	18	18	18
MEAN	3.50	4.00	5.01	6.00	7.01	8.00	10.00	12.00	24.02
SD	0.02	0.00	0.04	0.00	0.03	0.00	0.00	0.00	0.09
CV(%)	0.56	0.00	0.79	0.00	0.45	0.00	0.00	0.00	0.36
MAX	3.58	4.00	5.17	6.00	7.13	8.00	10.00	12.00	24.37
MIN	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00

Table 7

Plasma Concentration of Pyridostigmina Following Oral Pyridostigmina^{1,2}

SUBJ#	SCHEDULED TIME OF SAMPLE									
	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	2.50	3.00
	PYRIDOSTIGMINE CONCENTRATION ng/ml									
7	0.00	0.00	6.43	8.24	8.33	8.69	12.30	9.72	9.63	13.80
8	0.00	0.00	2.21	6.44	5.14	4.72	6.56	8.03	7.15	12.20
9	0.00	0.00	2.27	3.95	4.01	5.46	6.01	4.91	4.76	4.21
10	0.00	0.00	0.00	2.33	2.66	3.28	3.56	4.57	4.54	7.26
11	0.00	5.11	12.70	17.20	19.30	23.70	19.90	16.30	14.60	14.80
12	0.00	0.00	5.67	4.49	6.28	7.04	11.70	13.90	13.20	8.75
13	0.00	0.00	7.61	13.50	12.80	16.80	14.40	14.30	16.70	13.50
14	0.00	3.51	4.98	10.70	14.50	10.00	9.07	16.20	20.90	14.00
15	0.00	0.00	0.00	5.14	7.83	10.90	14.60	12.30	10.90	13.50
16	0.00	0.00	0.00	0.00	0.00	1.67	3.75	10.20	5.90	7.96
17	0.00	0.00	7.75	10.60	11.10	13.80	10.20	10.50	9.42	8.37
18	0.00	0.00	8.04	17.90	14.80	11.80	11.90	7.74	6.01	5.26
19	0.00	4.16	15.40	8.17	13.30	11.00	8.45	8.39	6.22	5.04
20	0.00	0.00	5.62	8.17*	6.30	9.86	14.00	13.60	10.30	12.10
21	0.00	1.93*	5.02	8.58	11.50	9.74	10.10	10.90	5.56	7.35
22	0.00	2.81	6.13	14.10	11.40	9.23	10.10	7.57	8.17	8.17
23	0.00	4.80	7.77	10.90	14.00	16.10	15.30	13.90	13.40	12.30
24	0.00	2.00	10.60	10.90	11.60	10.00	13.00	10.60	9.38	9.98
#	18	18	18	18	18	18	18	18	18	18
MEAN	0.00	1.35	6.01	8.96	9.71	10.21	10.83	10.76	9.82	9.92
SD	0.00	1.90	4.24	4.85	4.97	5.22	4.22	3.51	4.49	3.42
CV(%)	ERR	140.82	70.59	54.15	51.13	51.17	38.97	32.62	45.77	34.51
MAX	0.00	5.11	15.40	17.90	19.30	23.70	19.90	16.30	20.90	14.80
MIN	0.00	0.00	0.00	0.00	0.00	1.67	3.56	4.57	4.54	4.21

SUBJ#	SCHEDULED TIME OF SAMPLE									
	3.50	4.00	5.00	6.00	7.00	8.00	10.00	12.00	24.00	
	PYRIDOSTIGMINE CONCENTRATION ng/ml									
7	10.90	8.48	5.08	2.69	4.25	0.00	0.00	0.00	0.00	
8	9.30	9.24	4.96	3.22	2.24*	1.80	0.00	0.00	0.00	
9	5.00	6.19	6.65	2.11	1.75*	0.00	0.00	0.00	0.00	
10	6.62	5.67	5.76	2.01	2.21	0.00	0.00	0.00	0.00*	
11	9.84	11.90	9.18	7.99	6.88	5.08	2.04	0.00	0.00	
12	12.20	10.20	6.62	4.10	2.70	2.50	0.00	0.00	0.00	
13	13.40	11.10	16.20	5.55	3.17	4.21	0.00	0.00	0.00	
14	13.90	11.60	12.70	7.59	6.45		0.00	1.92	0.00	
15	12.00	13.20	11.50	6.22	2.56	0.00	0.00	0.00	0.00	
16	5.30	7.53	7.02	6.28	4.61	3.57	2.20	0.00	0.00	
17	6.28*	6.53	4.69*	3.52	0.00	0.00	0.00	0.00	0.00	
18	4.28	3.45	3.06	0.00	0.00	0.00	0.00	0.00	0.00	
19	3.74	5.38	3.99	7.02	2.59	1.78	0.00	0.00	0.00	
20	12.10	8.14	5.45	4.07	5.90	5.50	4.58	1.58	0.00	
21	3.76	5.70	2.33	3.90	3.34	0.00	0.00	0.00	0.00	
22	7.67	5.91	4.77	3.56	0.00	1.93	0.00	0.00	0.00	
23	13.10	8.57	7.46	4.89	4.60	5.29	1.69	0.00	2.20	
24	9.04	9.45	4.62	3.41	2.63	2.13	1.84	0.00	0.00	
#	18	18	18	18	18	17	18	18	18	
MEAN	8.80	8.24	6.78	4.34	3.10	1.99	0.69	0.19	0.12	
SD	3.55	2.67	3.56	2.11	2.06	2.07	1.28	0.57	0.52	
CV(%)	40.37	32.42	52.56	48.65	66.47	109.63	186.20	292.58	424.26	
MAX	13.90	13.20	16.20	7.99	6.88	5.50	4.58	1.92	2.20	
MIN	3.74	3.45	2.33	0.00	0.00	0.00	0.00	0.00	0.00	

* Sample was not obtained at the scheduled time. See Table 6 for the time of sample.
 1 Concentrations are nanograms of pyridostigmina base/ml
 2 Concentrations less than 1.5 ng/ml, the lower limit of detectability of the assay are denoted 0.00

Table 8

Indicators of "Goodness of Fit" for the Pharmacokinetic
Curve Fitting

SUB #	IV		PO	
	SUM of WEIGHTED SQUARED RESIDUALS	CORREL	SUM of WEIGHTED SQUARED RESIDUALS	CORREL
7	3.134	.976	4.221	.924
8	2.192	.985	7.625	.846
9	1.664	.989	3.591	.878
10	1.803	.961	3.990	.822
11	2.425	.989	2.718	.973
12	7.669	.967	7.514	.888
13	13.916	.928	2.402	.971
14	3.366	.987	8.474	.891
15	4.277	.967	4.609	.948
16	1.604	.983	2.253	.959
17	1.375	.984	.652	.984
18	1.987	.974	.648	.990
19	1.551	.987	4.088	.908
20	3.677	.981	6.431	.911
21	1.348	.988	4.971	.904
22	2.351	.988	2.633	.934
23	5.649	.933	2.745	.971
24	2.098	.988	2.294	.971
AVG	3.449	.975	3.992	.926
STD DEV	3.091	.018	2.288	.049

Table 9

Estimates of the Pharmacokinetic Microconstants for Pyridostigmine

SUB #	VOL L	K10 hr ⁻¹	K12 hr ⁻¹	K21 hr ⁻¹	K01 hr ⁻¹	BIOAVA	TLAG hr
7	12.969	3.150	5.740	1.927	.367	.254	.347
8	33.444	1.535	.976	1.337	.284	.265	.391
9	23.227	2.077	1.811	1.043	.236	.194	.359
10	42.990	2.109	2.350	1.523	.193	.393	.596
11	20.739	1.106	1.478	.584	.580	.250	.174
12	20.965	1.819	1.685	1.711	.292	.248	.341
13	10.687	3.707	1.483	1.259	.268	.341	.388
14	14.074	3.064	1.655	1.016	.188	.511	.202
15	13.739	3.394	4.141	1.389	.306	.371	.673
16	6.683	9.994	24.961	7.802	.149	.387	1.305
17	11.882	5.649	4.655	3.323	.310	.354	.332
18	16.691	1.985	2.849	.607	1.441	.147	.422
19	10.209	4.804	5.261	3.046	.334	.213	.151
20	13.529	2.915	2.618	1.543	.202	.333	.346
21	8.642	5.959	4.995	3.263	.272	.244	.223
22	17.323	2.081	2.201	.731	.503	.186	.229
23	19.976	2.180	2.429	1.985	.298	.355	.145
24	16.592	2.000	2.485	.922	.495	.203	.213
AVG	17.465	3.307	4.098	1.945	.373	.292	.380
STD DEV	8.930	2.159	5.405	1.690	.290	.094	.272

Table 10

Estimates of the Pharmacokinetic Macroconstants for Pyridostigmine

SUB #	ALPHA hr ⁻¹	BETA hr ⁻¹	A(IV) ng/ml	B(IV) ng/ml	A(PO) ng/ml	B(PO) ng/ml	C(PO) ng/ml
7	10.223	.594	-11.706	-32.391	-6.285	-43.960	50.093
8	3.208	.640	-34.992	-65.396	-5.645	-17.281	22.980
9	4.444	.488	-15.358	-22.867	-4.161	-11.372	15.494
10	5.386	.596	-6.399	-13.867	-2.812	-8.691	11.491
11	2.950	.219	-26.573	-55.226	-26.227	26.594	-.335
12	4.528	.687	-18.174	-43.529	-6.169	-24.042	30.173
13	5.618	.830	-27.758	-18.440	-14.972	-13.974	29.057
14	5.128	.607	-29.098	-24.435	-12.759	-14.951	27.737
15	8.360	.564	-13.484	-23.667	-9.336	-34.505	43.876
16	40.848	1.909	-5.909	-22.550	-1.812	-7.473	9.279
17	12.072	1.555	-9.726	-15.260	-6.757	-12.900	19.690
18	5.210	.231	-16.513	-30.374	-32.303	8.219	24.118
19	11.880	1.232	-12.689	-25.133	-5.154	-13.611	18.725
20	6.370	.706	-18.533	-28.984	-7.083	-15.037	22.073
21	12.683	1.533	-12.953	-19.682	-5.417	-9.791	15.198
22	4.688	.324	-24.370	-36.178	-12.111	29.152	-16.965
23	5.855	.739	-12.401	-31.626	-7.523	-30.530	37.962
24	5.042	.366	-17.336	-32.261	-11.993	57.001	-45.109
AVG	8.583	.768	-17.443	-30.104	-9.918	-7.620	17.530
STD DEV	8.610	.479	8.116	13.381	7.940	24.391	21.983

Table 11

Estimates of the Area Under the Concentration-Time Curve and Clearance of Pyridostigmine

SUB #	AUC(IV) ng-hr/ml	AUC(PO) ng-hr/ml	DOSE(IV) ug	DOSE(PO) ug	CL ml/min	CL ml/min/kg	CL ml/ml GFR
7	22.05	62.14	900.73	9995.15	680.85	8.46	5.61
8	16.77	52.02	860.66	10095.00	855.61	11.27	7.97
9	19.11	41.54	922.14	10328.41	804.11	10.51	5.29
10	10.13	44.45	918.63	10248.01	1510.95	19.62	13.36
11	40.90	111.81	938.26	10257.15	382.34	4.96	2.59
12	25.73	67.06	980.98	10300.24	635.43	8.02	4.53
13	23.10	88.70	915.16	10309.44	660.32	10.53	7.11
14	22.32	120.34	962.67	10158.16	718.74	8.31	5.32
15	18.58	80.98	866.09	10187.92	777.07	9.81	5.40
16	14.23	58.36	950.27	10065.18	1113.07	10.62	6.77
17	12.49	54.63	838.53	10361.55	1118.67	17.21	10.20
18	23.44	46.02	776.69	10391.74	552.16	7.01	4.41
19	18.91	44.70	927.57	10272.74	817.49	13.27	7.36
20	23.76	86.86	936.95	10291.64	657.29	8.63	4.74
21	16.32	49.13	840.21	10355.23	858.22	11.87	6.42
22	25.25	53.39	910.13	10320.92	600.77	8.57	5.16
23	22.01	84.95	958.80	10412.92	725.90	8.75	5.00
24	24.80	62.50	823.07	10231.68	553.18	8.14	5.71
AVG	21.11	67.20	901.53	10254.62	779.01	10.31	6.27
STD DEV	6.70	23.43	55.50	115.06	258.29	3.53	2.42

Table 12

Amounts of Pyridostigmine Base Recovered in the Urine
After Intravenous¹ and Oral² Administration of Pyridostigmine Bromide
(micrograms)

SCHEDULED ROUTE INTERVAL	17	18	19	20	21	22	23	24	MEAN	SD	CV(%)	MAX	MIN
BLANK	IV	NA	NA	NA	NA	NA	NA	NA					
0.00-1.00	IV	211	241	366	232	187	188	403	248	89	36	403	158
1.00-2.00	IV	272	162	0	116	68	69	67	104	82	79	272	0
2.00-4.00	IV	102	29	101	0	30	52	50	50	36	71	102	0
4.00-6.00	IV	16	4	42	85	4	14	27	27	27	101	85	4
6.00-8.00	IV	7	1	0	23	1	2	9	7	8	114	23	0
8.00-24.0	IV	32	0	279	53	90	0	0	60	94	157	279	0
TOTAL EXCRETED		640	438	788	510	379	326	556	495	163	33	788	324

SCHEDULED ROUTE INTERVAL	17	18	19	20	21	22	23	24	MEAN	SD	CV(%)	MAX	MIN
BLANK	PO	NA	NA	NA	NA	NA	NA	NA					
0.00-1.00	PO	134	126	168	62	85	235	32	108	73	68	235	18
1.00-2.00	PO	420	185	161	207	220	267	319	255	84	33	420	161
2.00-4.00	PO	602	149	256	305	111	199	242	280	154	55	602	111
4.00-6.00	PO	382	37	68	261	15	97	155	159	129	81	382	15
6.00-8.00	PO	123	9	125	183	4	58	117	84	63	75	183	4
8.00-24.0	PO	395	192	96	245	66	88	340	206	121	58	395	66
TOTAL EXCRETED		2056	698	873	1263	501	943	1207	1091	471	43	2056	501

1 1.32 mg of pyridostigmine bromide infused over 30 minutes

2 16 mg of pyridostigmine bromide administered as Mestinon^R syrup

Table 13

Recovery of Pyridostigmine in the Urine after
Intravenous and Oral Administration of
Pyridostigmine Bromide

SUBJ #	INTRAVENOUS ADMINISTRATION			ORAL ADMINISTRATION		
	URINARY RECOVERY-ug	DOSE ug	% EXCRETED	URINARY RECOVERY-ug	DOSE ug	% EXCRETED
17	640	839	76.3	2056	10362	19.8
18	438	777	56.4	698	10392	6.7
19	788	928	84.9	873	10273	8.5
20	510	937	54.4	1263	10292	12.3
21	379	840	45.1	501	10355	4.8
22	326	910	35.8	943	10321	9.1
23	324	959	33.8	1189	10413	11.4
24	556	823	67.6	1207	10232	11.8
MEAN	495	877	56.8	1091	10330	10.6
SD	163	65	18.5	471	62	4.6
CV (%)	33	7	32.6	43	1	43.1
MAX	788	959	84.9	2056	10413	19.8
MIN	324	777	33.8	501	10232	4.8

Table 14

Pyridostigmine Renal Clearance and Bioavailability
Calculated Using Urinary Excretion Data

SUBJ#	RENAL CLEARANCE ¹ ml/min	BIOAVAILABILITY ² %
17	854	26.0 (35.4) ³
18	311	11.9 (14.7)
19	694	10.0 (21.3)
20	357	22.5 (33.3)
21	387	10.7 (24.4)
22	215	25.5 (18.6)
23	245	33.8 (35.5)
24	374	17.5 (20.3)
MEAN	430	19.7 (29.2)
SD	225	8.6 (9.4)
CV(%)	52	43.7 (32.2)
MAX	854	33.8 (35.5)
MIN	215	10.0 (14.7)

¹ Calculated from the total clearance times the fractional excretion of unchanged pyridostigmine into the urine.

² Calculated by dividing the fractional excretion of pyridostigmine into the urine after oral dosing by the fractional excretion of urine into the urine after intravenous dosing.

³ Values in () represent the parameter estimate of bio-availability determined from the curve fitting process (Table 9).

Table 15

Inhibition of Erythrocyte Acetylcholinesterase During and Following Intravenous Pyridostigmine

SUBJ#	SCHEDULED TIME OF SAMPLE											
	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	3.00	4.00	6.00	24.00
	INHIBITION OF ERYTHROCYTE ACETYLCHOLINESTERASE											
7	0.00	0.18	0.29	0.26	0.23	0.18	0.15	0.12	0.08	0.05	0.03	-0.02
8	0.00	0.22	0.28	0.22	0.18	0.12	0.09	0.08	0.06	0.00	-0.03	-0.03
9	0.00	0.14	0.27	0.29	0.23	0.21	0.17	0.13	0.10	0.06	0.01	0.04
10	0.00	0.14	0.26	0.22	0.17	0.16	0.14	0.10	0.09	0.04	-0.02	-0.04
11	0.00	0.13	0.29	0.28	0.25	0.21	0.14	0.14	0.06	0.02	0.02	-0.03
12	0.00	0.20	0.33	0.29	0.24	0.24	0.11	0.13	0.11	0.05	0.03	-0.03
13	0.00	0.19	0.39	0.24	0.20	0.13	0.09	0.06	0.06	0.02	0.00*	-0.01
14	0.00	0.20	0.32	0.25	0.18	0.14	0.10	0.06	0.06	0.01	-0.01	0.02
15	0.00	0.18	0.28	0.24	0.22	0.16	0.15	0.10	0.06	0.01	0.01	0.02
16	0.00	0.17	0.26*	0.24	0.19	0.15	0.12	0.11	0.11	0.01	0.01	0.03
17	0.00	0.16	0.29	0.24	0.19	0.12	0.09	0.07	0.04	0.03	0.00	0.03
18	0.00	0.12	0.22	0.19	0.14	0.10	0.06	0.05	0.05	0.00	0.00	0.01
19	0.00	0.19	0.36	0.29	0.28	0.23	0.16	0.13	0.07	0.05	0.03	0.02*
20	0.00	0.19	0.32	0.27	0.23	0.19	0.15	0.12	0.06	0.03	0.02	0.00*
21	0.00	0.17	0.29	0.22	0.16	0.12	0.10	0.06	0.06	0.04	0.01	0.00
22	0.00	0.21	0.30	0.23	0.18	0.14	0.10	0.09	0.05	0.03	0.01	0.00
23	0.00	0.15	0.29	0.27	0.19	0.17	0.15	0.10	0.07	0.03	0.05	-0.01
24	0.00	0.14	0.31	0.23	0.19	0.16	0.12	0.12	0.07	0.03	0.02	-0.04
#	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.00	0.17	0.30	0.25	0.20	0.16	0.12	0.10	0.07	0.03	0.01	0.00
SD	0.00	0.03	0.04	0.03	0.04	0.04	0.03	0.03	0.02	0.02	0.02	0.03
CV(%)	0.00	17.11	12.94	11.58	17.40	24.83	25.25	29.44	28.99	63.19	182.29	1150.45
MAX	0.00	0.22	0.39	0.29	0.28	0.24	0.17	0.14	0.11	0.06	0.05	0.04
MIN	0.00	0.12	0.22	0.19	0.14	0.10	0.06	0.05	0.04	0.00	-0.03	-0.04

*

Sample was not obtained at the scheduled time. See Table 4 for the time of sample.

Table 16

Inhibition of Erythrocyte Acetylcholinesterase Following Oral Pyridostigmine

SUBJ#	SCHEDULED TIME OF SAMPLE													
	0.00	0.25	0.50	0.75	1.00	1.33	1.67	2.00	3.00	4.00	6.00	8.00	10.00	24.00
	INHIBITION OF ERYTHROCYTE ACETYLCHOLINESTERASE (%)													
7	0.00	0.02	0.11	0.14	0.17	0.19	0.27	0.29	0.31	0.26	0.16	0.11	0.06	0.02
8	0.00	0.01	0.04	0.10	0.11	0.10	0.19	0.20	0.26	0.25	0.11	0.07	0.05	0.00
9	0.00	0.03	0.06	0.10	0.11	0.14	0.14	0.17	0.19	0.22	0.14	0.08	0.08	0.01
10	0.00	0.03	0.05	0.08	0.10	0.14	0.17	0.21	0.25	0.22	0.11	0.06	0.04	0.02
11	0.00	-0.01	0.12	0.22	0.31	0.34	0.34	0.29	0.29	0.25	0.17	0.10	0.05	-0.01
12	0.00	-0.02	0.07	0.11	0.14	0.18	0.23	0.27	0.30	0.25	0.11	0.07	0.02	-0.03
13	0.00	0.00	0.12	0.20	0.28	0.33	0.33	0.32	0.35	0.34	0.18	0.13	0.08	-0.02
14	0.00	-0.01	0.04	0.17	0.25	0.27	0.28	0.32	0.31	0.30	0.21	0.12	0.09	-0.04
15	0.00	0.02	0.01	0.06	0.14	0.22	0.27	0.33	0.39	0.36	0.22	0.11	0.07	-0.04
16	0.00	0.01	0.00	-0.01	-0.01	0.02	0.07	0.14	0.20	0.19	0.20	0.14	0.08	-0.01
17	0.00	-0.01	0.09	0.18	0.23	0.29	0.31	0.30	0.28	0.26	0.13	0.09	0.04	0.00
18	0.00	0.01	0.09	0.18	0.20	0.22	0.21	0.20	0.17	0.15	0.05	0.03	0.02	-0.04
19	0.00	0.10	0.20	0.26	0.31	0.30	0.27	0.25	0.21	0.17	0.12	0.07	0.08	0.01
20	0.00	0.00	0.07	0.11	0.15	0.17	0.21	0.25	0.29	0.23	0.16	0.07	0.09	0.01
21	0.00	-0.01	0.05	0.10	0.16	0.18	0.20	0.22	0.17	0.14	0.06	0.05	0.05	0.00
22	0.00	0.04	0.11	0.18	0.27	0.26	0.23	0.25	0.27	0.22	0.10	0.06	0.04	-0.01
23	0.00	0.04	0.11	0.15	0.21	0.24	0.26	0.25	0.27	0.23	0.15	0.13	0.08	0.01
24	0.00	-0.01	0.15	0.17	0.25	0.25	0.30	0.31	0.26	0.21	0.12	0.08	0.11	0.04
#	18	18	18	18	18	18	18	18	18	18	18	18	18	18
MEAN	0.00	0.01	0.08	0.14	0.19	0.21	0.24	0.25	0.27	0.24	0.14	0.09	0.06	0.00
SD	0.00	0.03	0.05	0.06	0.08	0.08	0.07	0.06	0.06	0.06	0.05	0.03	0.03	0.02
CV(%)	0.00	213.69	60.16	46.26	44.99	38.75	29.05	21.71	22.58	24.44	34.03	35.35	40.45	513.21
MAX	0.00	0.10	0.20	0.26	0.31	0.34	0.34	0.33	0.39	0.36	0.22	0.14	0.11	0.04
MIN	0.00	-0.02	0.00	-0.01	-0.01	0.02	0.07	0.14	0.17	0.14	0.05	0.03	0.02	-0.04

*

Sample was not obtained at the scheduled time. See Table 6 for the time of sample.

Table 17

Duration of Inhibition of Erythrocyte Acetylcholinesterase
After 1.3 mg of Pyridostigmine Bromide Intravenously

SUBJ#	EARLIEST TIME OF AChE INHIBITION ABOVE 20%	LATEST TIME OF AChE INHIBITION ABOVE 20%	DURATION OF AChE INHIBITION ABOVE 20% ¹
7	0.50	1.00	0.50
8	0.25	0.75	0.50
9	0.50	1.33	0.83
10	0.50	0.75	0.25
11	0.50	1.33	0.83
12	0.25	1.33	1.08
13	0.50	1.00	0.50
14	0.25	0.75	0.50
15	0.50	1.00	0.50
16	0.48	0.75	0.27
17	0.50	0.75	0.25
18	0.50	0.50	0.22 ²
19	0.50	1.33	0.83
20	0.50	1.00	0.50
21	0.50	0.75	0.25
22	0.25	0.75	0.50
23	0.50	0.75	0.25
24	0.50	0.75	0.25
MEAN	0.44	0.92	0.49
SD	0.11	0.26	0.25
CV(%)	24.01	28.06	52.09
MAX	0.50	1.33	1.08
MIN	0.25	0.50	0.22

¹ The method of determining duration for this table (except for Subject 18, see below) was by subtracting the time of the first measured value from the time of the last measured value over 20%. This is conservative in defining the actual duration of time above 20% and should be considered at least likely to be an underestimate of the true duration.

² As mentioned in the text and shown in Table 15, Subject 18 had only one value in excess of 20%. Applying the method used elsewhere in this table would give a duration of 0 hours of inhibition in excess of 20% of baseline, which is clearly incorrect. In this subject's case only, the degree of inhibition was determined by linear interpolation using the values bounding the single measured inhibition of more than 20%.

Table 18

Duration of Inhibition of Erythrocyte Acetylcholinesterase
After 16 mg of Pyridostigmine Bromide Orally

SUBJ#	EARLIEST TIME OF AChE INHIBITION ABOVE 20%	LATEST TIME OF AChE INHIBITION ABOVE 20%	DURATION OF AChE INHIBITION ABOVE 20% ¹
7	1.67	4.00	2.33
8	2.00	4.00	2.00
9	4.00	4.00	1.17 ²
10	2.00	4.00	2.00
11	0.75	4.00	3.25
12	1.67	4.00	2.33
13	0.75	4.00	3.25
14	1.00	6.00	5.00
15	1.33	6.00	4.67
16	3.00	6.00 ³	3.00
17	1.00	4.00	3.00
18	1.00	2.00	1.00
19	0.50	3.00	2.50
20	1.67	4.00	2.33
21	1.67	2.00	0.33
22	1.00	4.00	3.00
23	1.00	4.00	3.00
24	1.00	4.00	3.00
MEAN	1.50	4.06	2.62
SD	0.87	1.11	1.15
CV(%)	57.76	27.37	43.80
MAX	4.00	6.00	5.00
MIN	0.50	2.00	0.33

¹ The method of determining duration for this table (except for Subject 9, see below) was by subtracting the time of the first measured value from the time of the last measured value over 20%. This is conservative in defining the actual duration of time above 20% and should be considered at least likely to be an underestimate of the true duration.

² As mentioned in the text and shown in Table 16, Subject 9 had only one value in excess of 20%. Applying the method used elsewhere in this table would give a duration of 0 hours of inhibition in excess of 20% of baseline, which is clearly incorrect. In this subject's case only, the degree of inhibition was determined by linear interpolation using the values bounding the single measured inhibition of more than 20%.

³ Inhibition at 4 hours was 19%.

Table 19

Maximal Inhibition of Erythrocyte Acetylcholinesterase
With 1.3 mg of Pyridostigmine Bromide Intravenously

SUBJECT #	MAXIMAL INHIBITION (%)
7	29
8	28
9	29
10	26
11	29
12	33
13	39
14	32
15	28
16	26
17	29
18	22
19	36
20	32
21	29
22	30
23	29
24	31
Mean	30
SD	3.8
CV (%)	12.7
MAX	39
MIN	22

Table 20

Maximal Inhibition of Erythrocyte Acetylcholinesterase
With 16 mg of Pyridostigmine Bromide Orally

SUBJECT #	MAXIMAL INHIBITION (%)	TIME AFTER DOSE TO PEAK INHIBITION (hrs)
7	31	3.0
8	26	3.0
9	22	4.0
10	25	3.0
11	34	1.67
12	30	3.0
13	35	3.0
14	32	2.0
15	39	3.0
16	20	3.0
17	31	1.67
18	22	1.33
19	31	1.0
20	29	3.0
21	22	2.0
22	27	3.0
23	27	3.0
24	31	2.0
Mean	29	2.5
SD	5.1	0.8
CV (%)	17.1	30.9
MAX	39	4.0
MIN	20	1.0

Table 21

Area within the Hysteresis Loop

SUB #	IV CURVE	PO CURVE
7	242.195	104.040
8	197.285	39.090
9	264.740	35.600
10	68.450	3.885
11	96.955	198.335
12	261.205	53.730
13	437.330	156.225
14	332.490	146.970
15	225.785	151.300
16	181.780	61.760
17	204.725	157.790
18	140.495	141.060
19	308.875	85.010
20	324.390	91.130
21	263.840	70.655
22	241.605	111.635
23	250.070	115.860
24	185.295	114.140
AVG	234.862	101.956
STD DEV	87.470	51.459
p vs zero	7.25×10^{-3}	0.048

Paired t, $p = 1.65 \times 10^{-5}$

Table 22

Indicators of "Goodness of Fit" for the Curve Fitting
to the Effect Model

SUB #	IV		PO	
	SUM of WEIGHTED SQUARED RESIDUALS	CORREL	SUM of WEIGHTED SQUARED RESIDUALS	CORREL
7	.0367	.998	4.0510	.938
8	.0197	.988	1.1140	.872
9	.0388	.987	9.0830	.920
10	.0691	.970	34.0136	.860
11	.0582	.979	.0234	.988
12	.1130	.964	.1220	.930
13	.1530	.965	.0982	.936
14	.0440	.972	.0698	.985
15	.0363	.982	5.0580	.962
16	.2340	.868	.2740	.958
17	.1580	.933	.0271	.988
18	.0182	.993	1.1620	.927
19	.9070	.987	.2280	.925
20	.0441	.988	.0853	.909
21	.2590	.817	.0530	.924
22	.0645	.985	.1160	.945
23	.3150	.969	.0631	.981
24	.0490	.967	.1280	.936
AVG	.1454	.9618	3.0983	.9380
STD DEV	.2097	.0467	8.0857	.0362

Table 23

Estimates of the Rate Constant of Exit from the Effect
Compartment and Pyridostigmine Concentration
that Produces 50% Inhibition of
Erythrocyte Acetylcholinesterase

SUBJ#	KEO /hr	IC50 ng/ml
7	3.756	27.563
8	4.624	30.165
9	2.621	22.066
10	4.530	18.345
11	3.399	41.063
12	3.330	31.484
13	5.761	30.934
14	2.759	37.632
15	3.205	26.721
16	1.278	23.126
17	1.890	22.308
18	4.571	39.738
19	3.067	17.307
20	3.237	33.916
21	1.222	33.386
22	5.728	31.013
23	3.186	33.398
24	3.395	30.116
AVG	3.420	29.460
STD DEV	1.284	6.842

Table 24

Indicators of "Goodness of Fit" for the Curve Fitting
to the Biochemical Model

SUB #	IV		ORAL	
	SUM of WEIGHTED SQUARED RESIDUALS	CORREL	SUM of WEIGHTED SQUARED RESIDUALS	CORREL
7	.00163	.995	.00890	.957
8	.00111	.991	.00688	.910
9	.00169	.986	.00905	.888
10	.00442	.960	.01416	.868
11	.00736	.969	.00394	.989
12	.00740	.968	.01050	.911
13	.00399	.967	.01390	.946
14	.00161	.987	.01040	.978
15	.00262	.975	.00603	.964
16	.00471	.907	.00212	.965
17	.00388	.988	.00255	.985
18	.00048	.993	.00547	.935
19	.00697	.979	.00789	.973
20	.00201	.984	.00954	.912
21	.00496	.972	.00245	.977
22	.00158	.981	.00600	.960
23	.00510	.984	.00483	.990
24	.00205	.971	.01120	.939
AVG	.00353	.97539	.00754	.94706
STD DEV	.00222	.01978	.00370	.03622

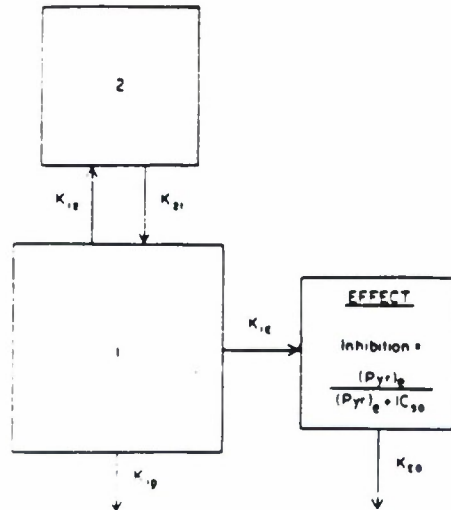
Table 25

Estimates of the Biochemical Rate Constants for Erythrocyte
Acetylcholinesterase Inactivation and Reactivation

SUB #	K(inact) (iv-fit)	K(inact) (po-fit)	K(inact) (AVG) ml/ng/hr	K(react) (iv-fit)	K(react) (po-fit)	K(react) (AVG) /hr
7	.092	.073	.083	2.729	1.933	2.331
8	.102	.063	.083	3.278	1.938	2.608
9	.077	.177	.127	1.860	4.455	3.158
10	.164	9.651*	.164	2.860	245.280*	2.860
11	.073	.067	.070	3.570	2.726	3.148
12	.095	.130	.113	3.202	5.012	4.107
13	.076	.118	.097	3.294	3.426	3.360
14	.071	.045	.058	2.968	1.634	2.301
15	.093	.089	.091	2.909	2.398	2.653
16	.053	.077	.065	1.488	1.948	1.718
17	.083	.093	.088	2.371	2.272	2.321
18	.079	.059	.069	3.596	2.394	2.995
19	.067	.589*	.067	1.652	13.984*	1.652
20	.073	.075	.074	2.495	2.912	2.704
21	.064	.051	.058	2.489	1.914	2.201
22	.096	.115	.105	3.799	3.335	3.567
23	.094	.060	.077	3.339	2.184	2.762
24	.087	.084	.086	3.160	2.440	2.800
AVG	.086	.076	.087	2.837	2.385	2.736
STD DEV	.024	.043	.027	.669	1.246	.616

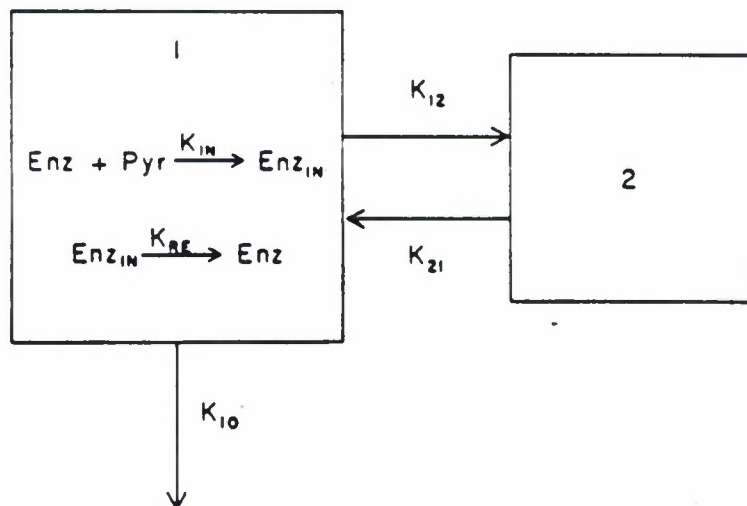
* Not included in the calculations of the average and standard deviation

Figure 1a



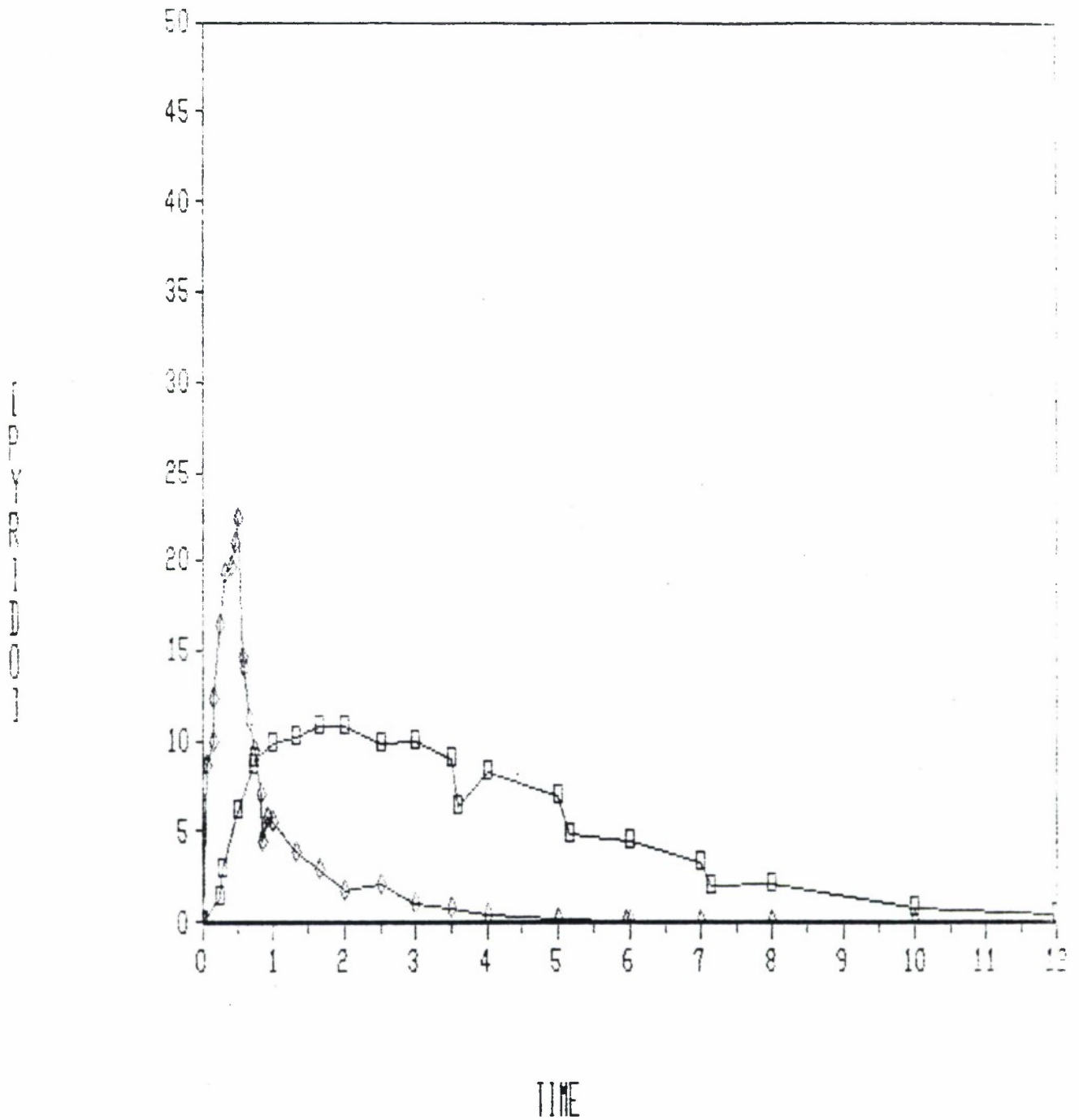
Schematic of the model used for the analysis of pyridostigmine effects assuming an effect compartment

Figure 1b



Schematic of the model used for the analysis of pyridostigmine effects using a biochemical model

Figure 2

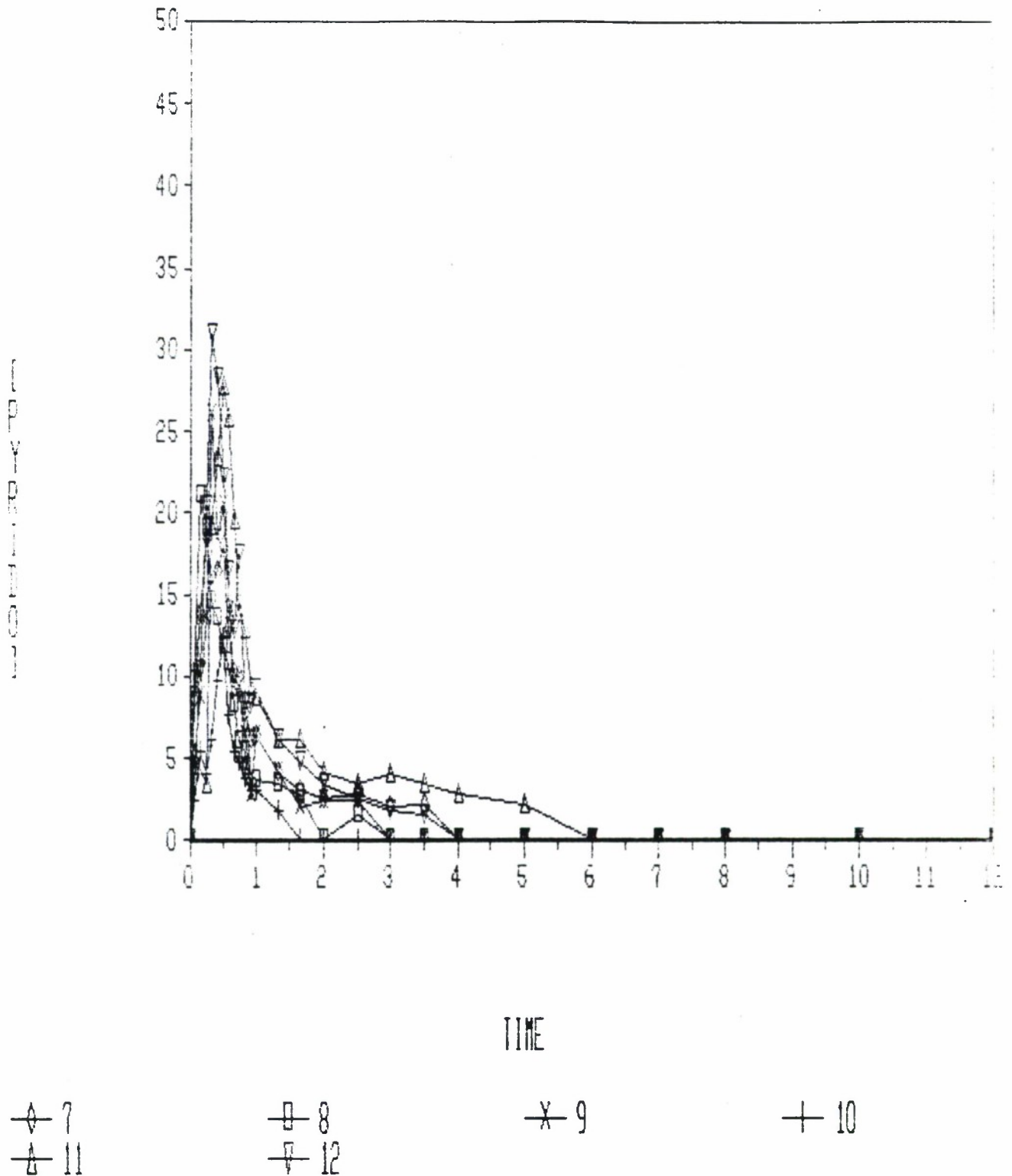


◆ IV

□ PO

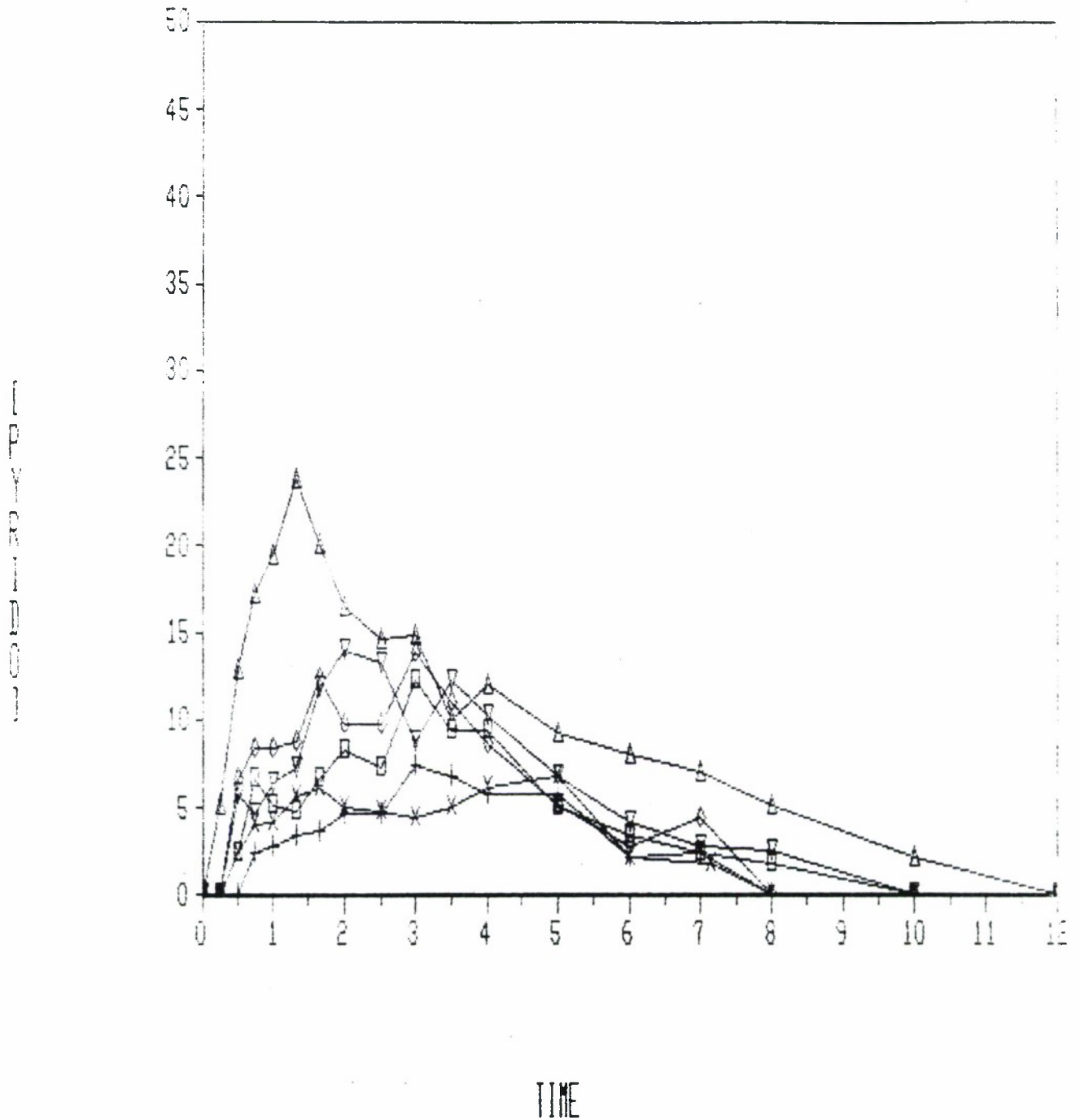
Average pyridostigmine base concentration in nanograms per milliliter for each sampling time after oral and intravenous administration of drug

Figure 2a



Time in hours after dosing
 Subjects 7 - 12: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after intravenous administration of drug

Figure 2b



◇ 7
△ 11

□ 8
▽ 12

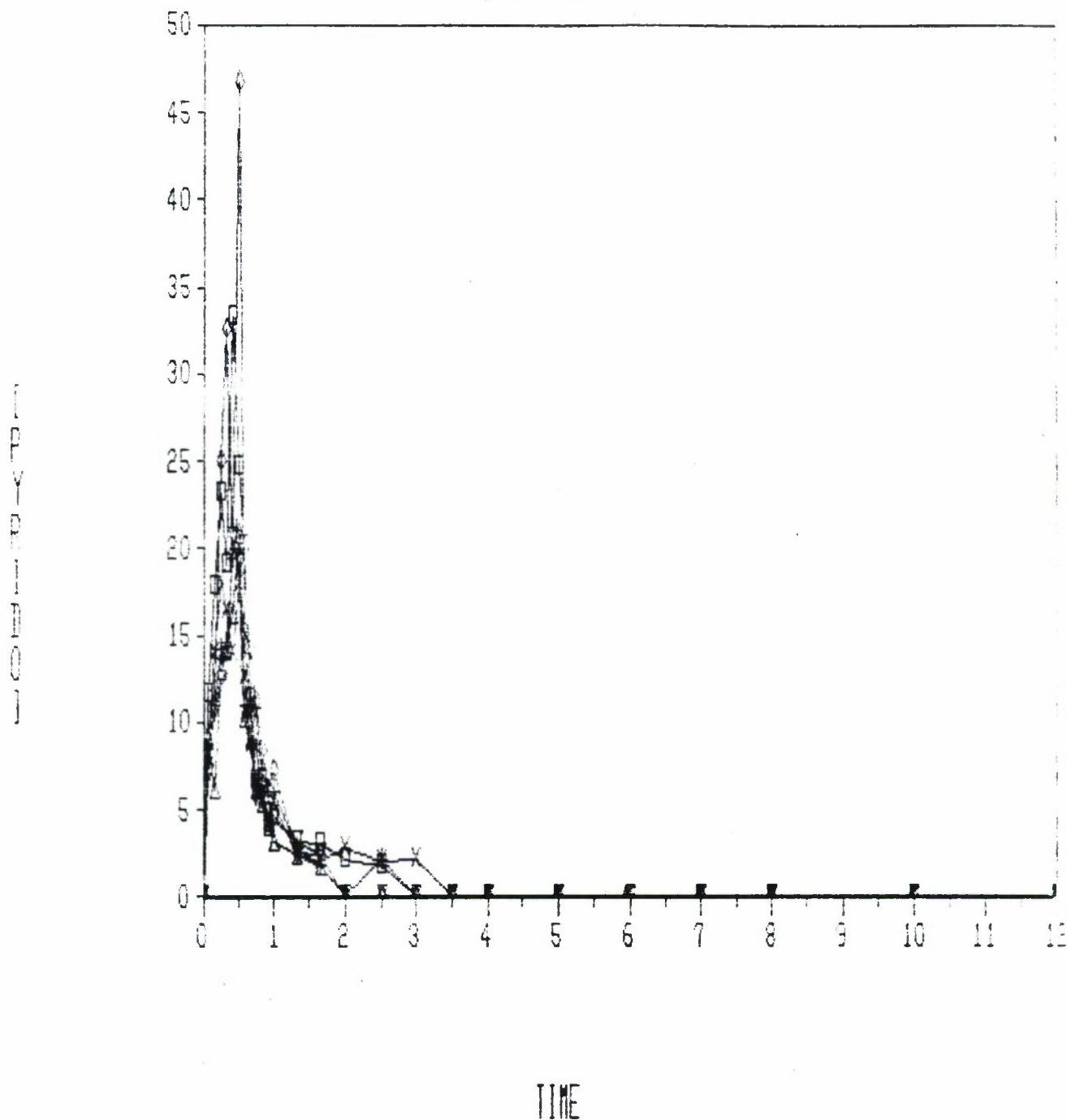
× 9

+ 10

Time in hours after dosing

Subjects 7 - 12: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after oral administration of drug

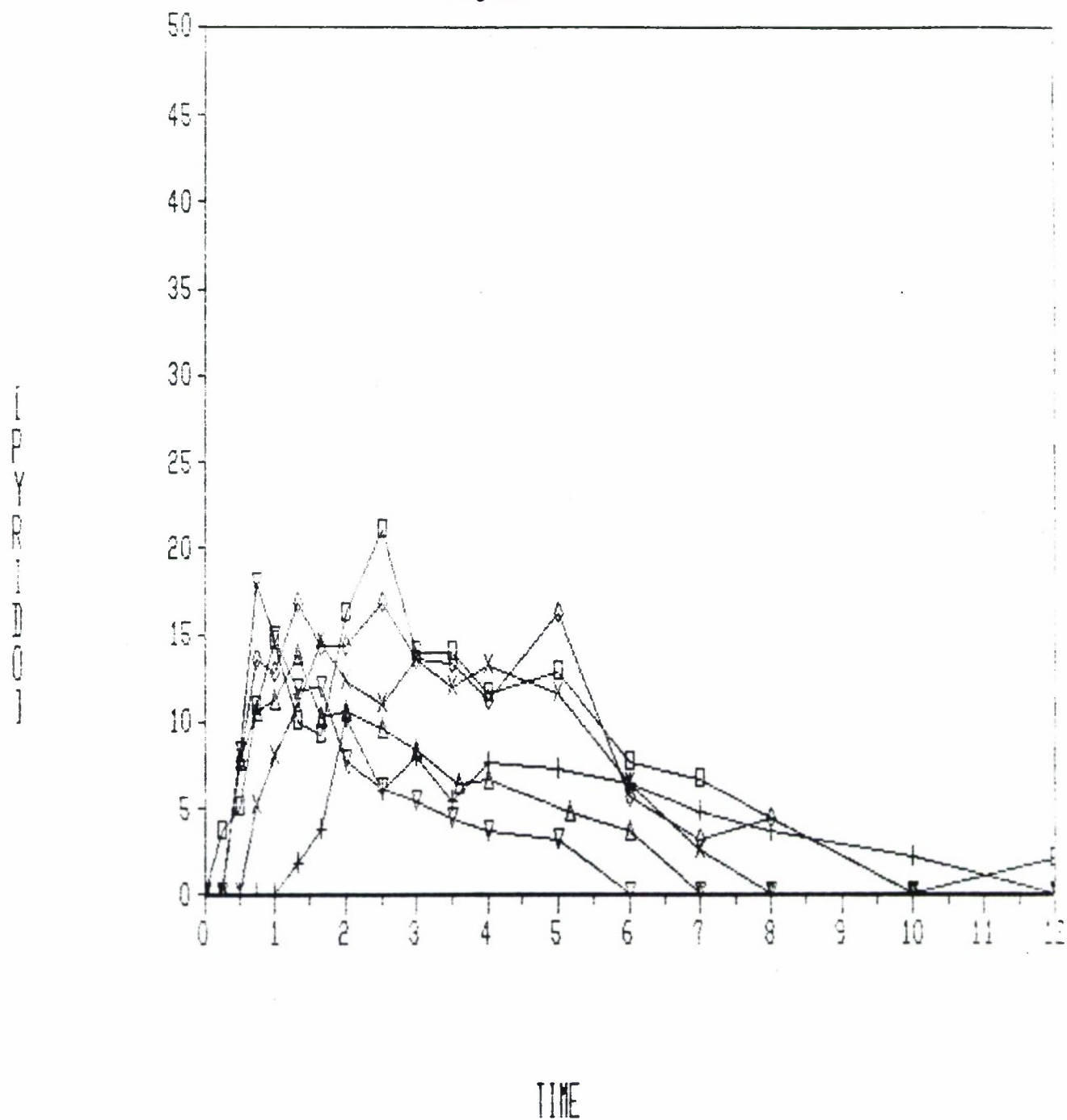
Figure 2c



◇ 13 □ 14 × 15 + 16
 △ 17 ▽ 18

Time in hours after dosing
 Subjects 13 - 18: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after intravenous administration of drug

Figure 2d



◇ 13
△ 17

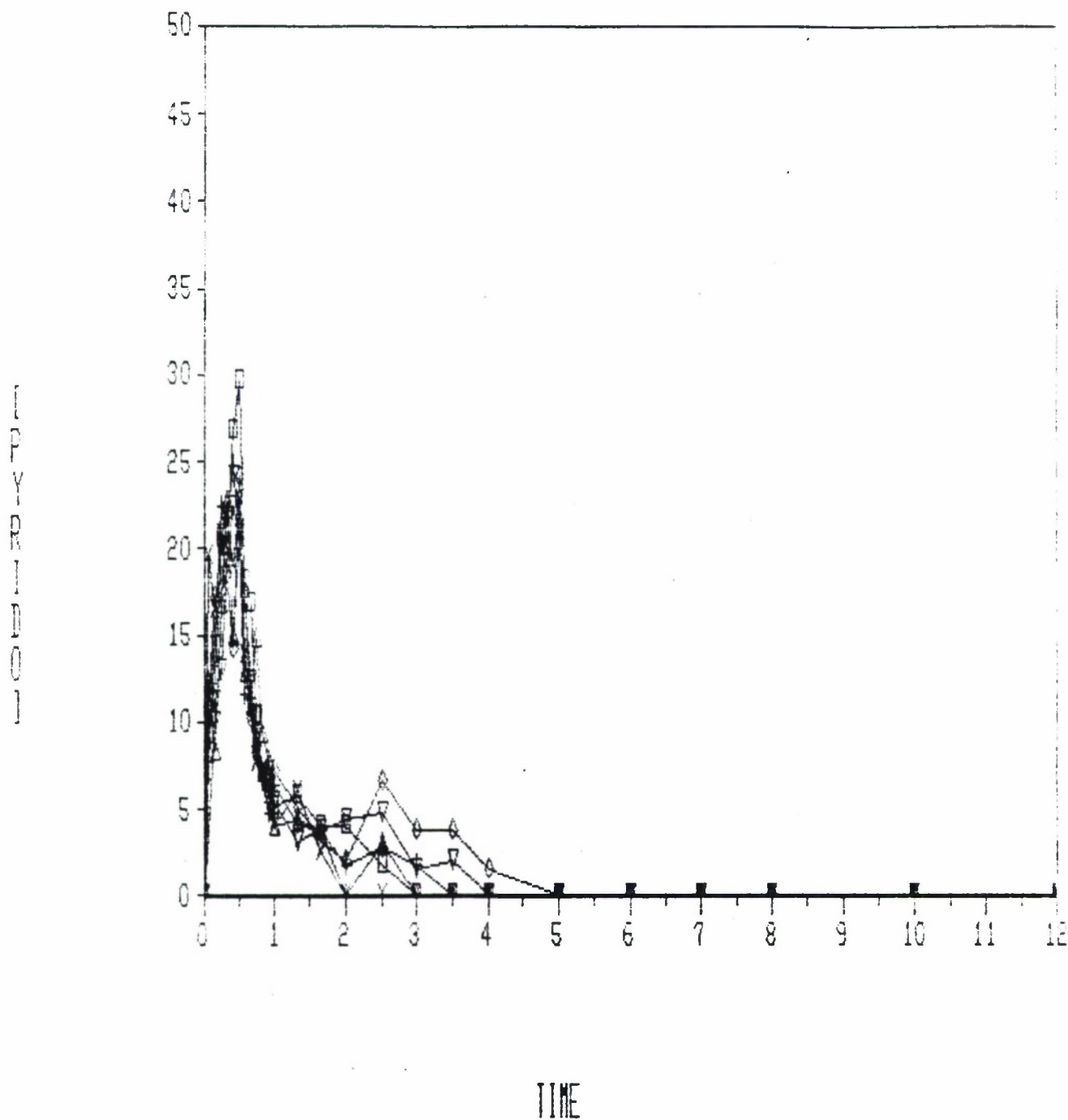
□ 14
▽ 18

× 15

+ 16

Time in hours after dosing
Subjects 13 - 18: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after oral administration of drug

Figure 2e



◇ 19
△ 23

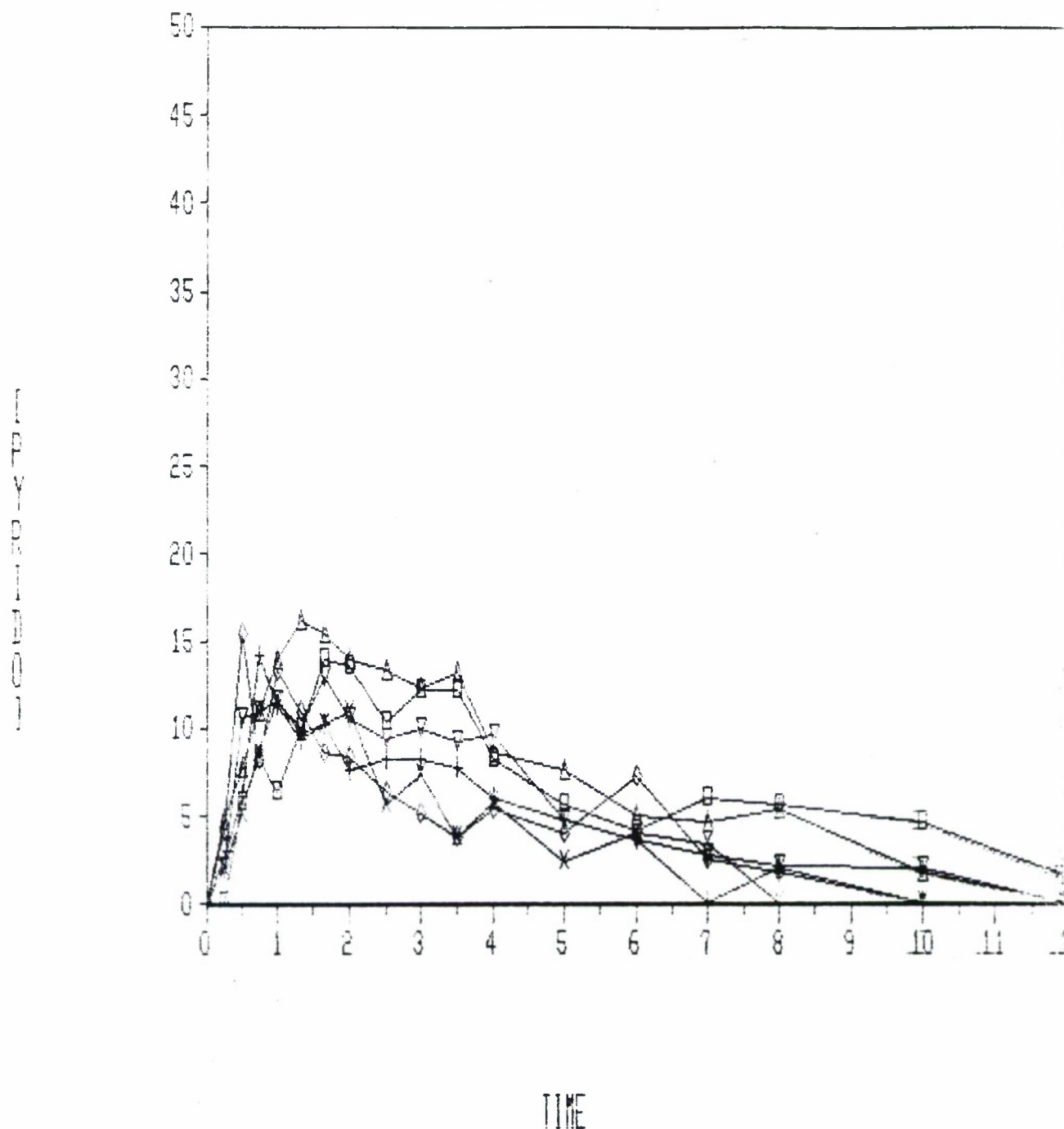
□ 20
▽ 24

× 21

+ 22

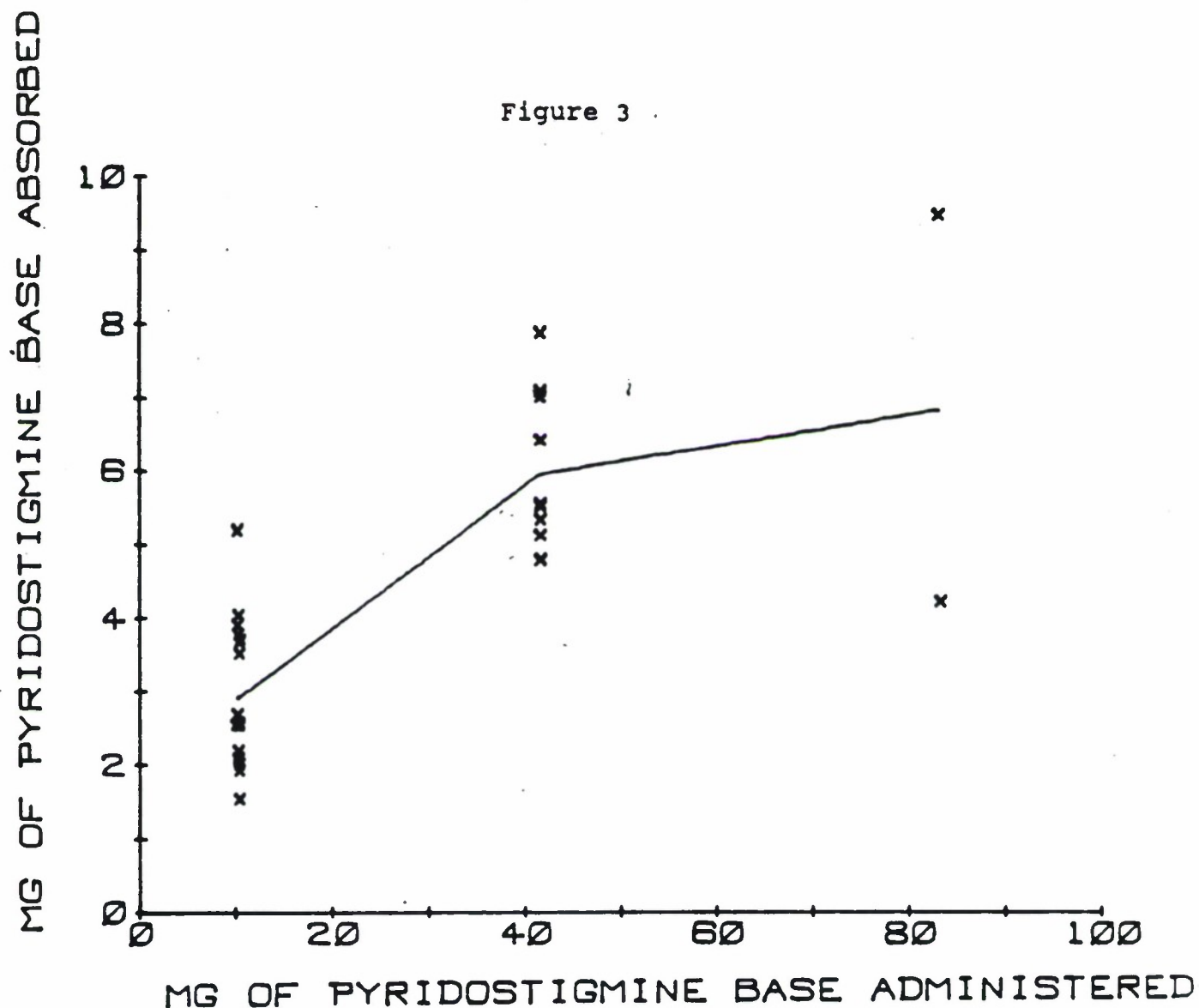
Time in hours after dosing
Subjects 19 - 24: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after intravenous administration of drug

Figure 2f



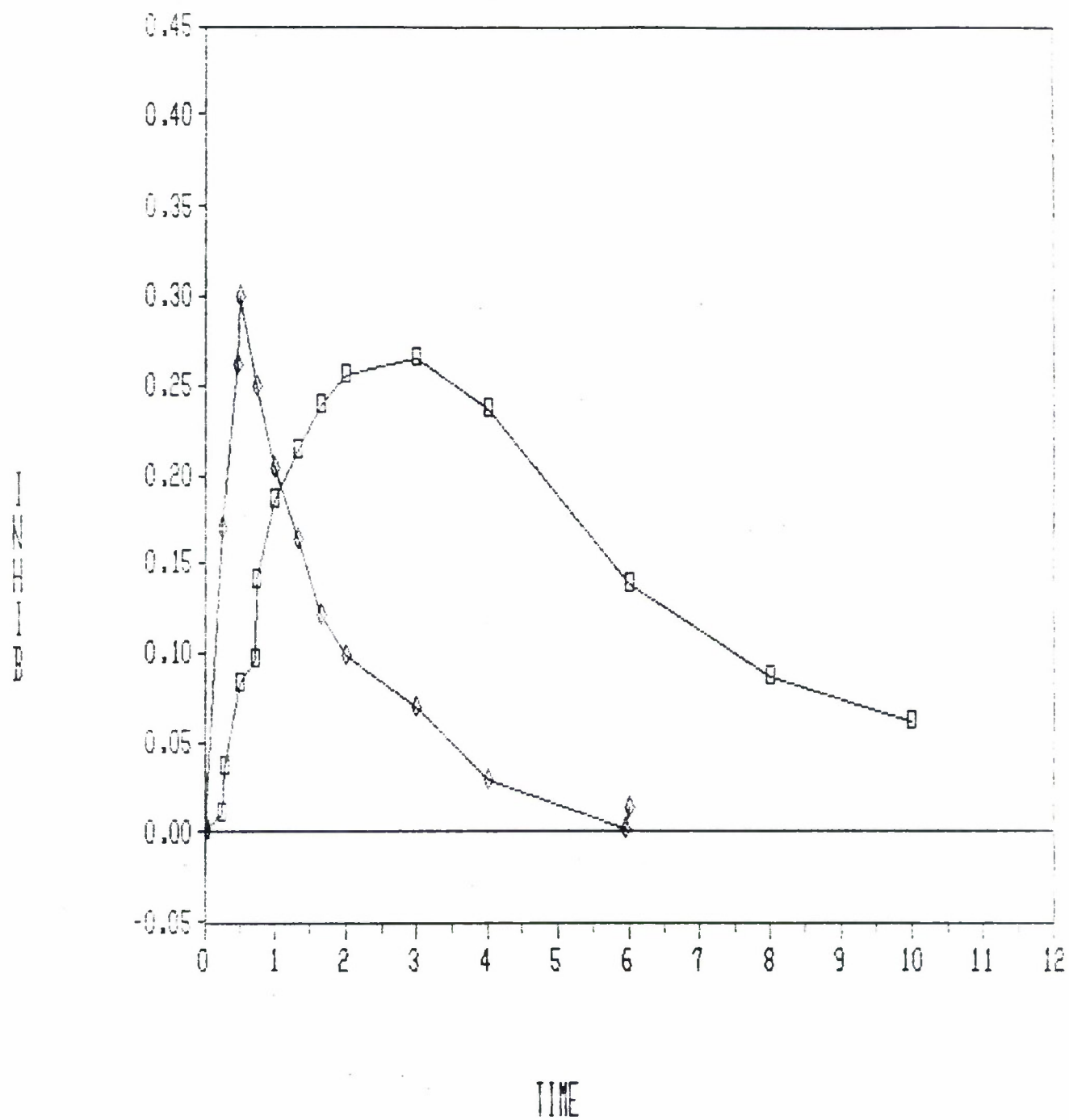
Δ 19 □ 20 × 21 + 22
 ▲ 23 ▽ 24

Time in hours after dosing
 Subjects 19 - 24: Concentrations of pyridostigmine base in nanograms per milliliter at each sampling time after oral administration of drug



Amount of pyridostigmine base absorbed plotted as a function of the size of the oral dose. X's are individual data points from subjects in whom pyridostigmine bioavailability was determined. The amount absorbed was calculated from the fraction available times the size of the oral dose. The 10.3 mg doses are from this study, the 41.6 mg doses are data from Breyer-Pfaff et al. Clin Pharmacol Ther 37:495,1985 and the 83.3 mg doses are calculated from the data of Aquilonius et al. Eur J Clin Pharmacol 18:423,1980.

Figure 4

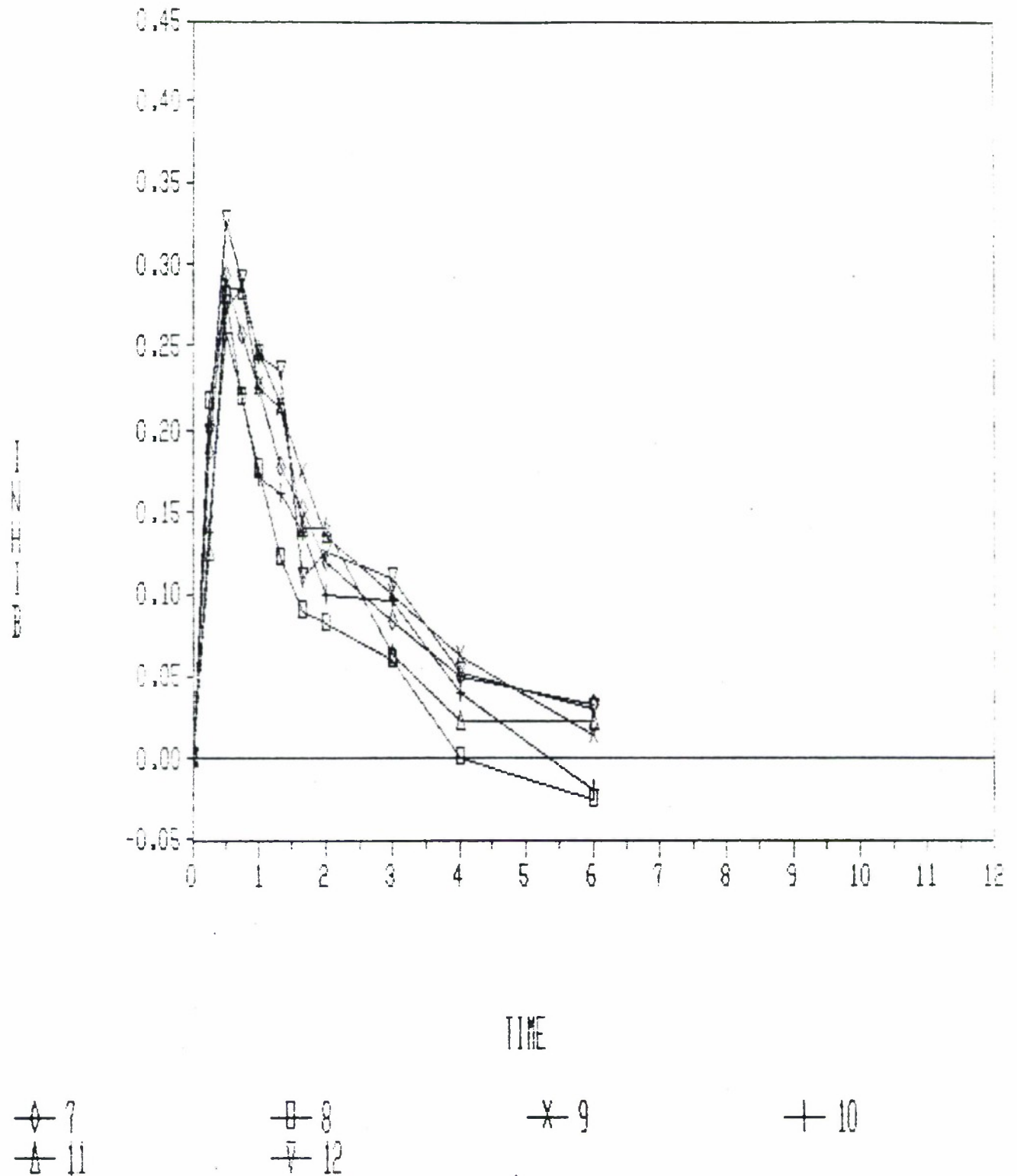


◆ IV

□ PO

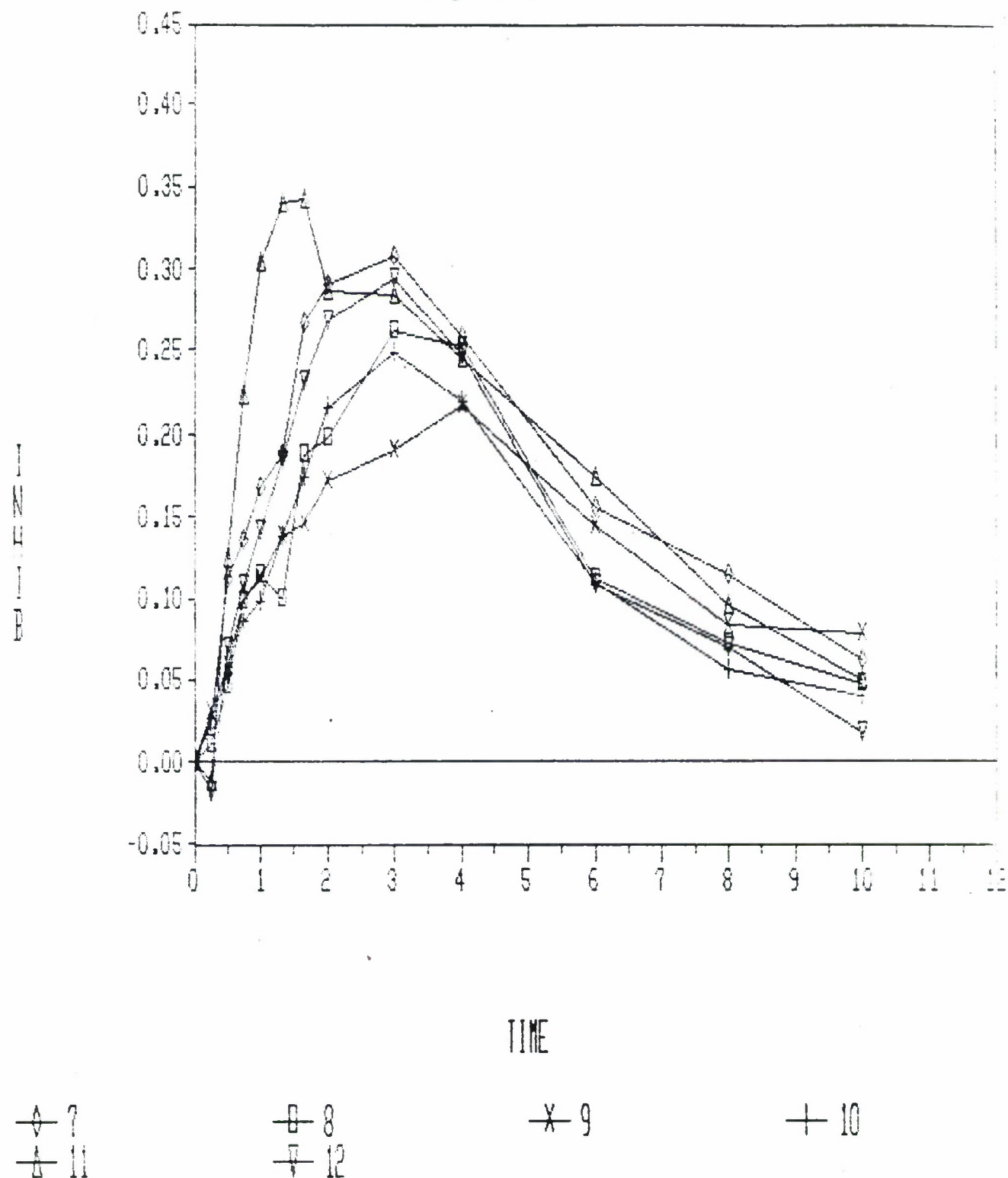
Average fractional inhibition of erythrocyte acetylcholinesterase for each sampling time after oral and after intravenous administration of drug

Figure 4a



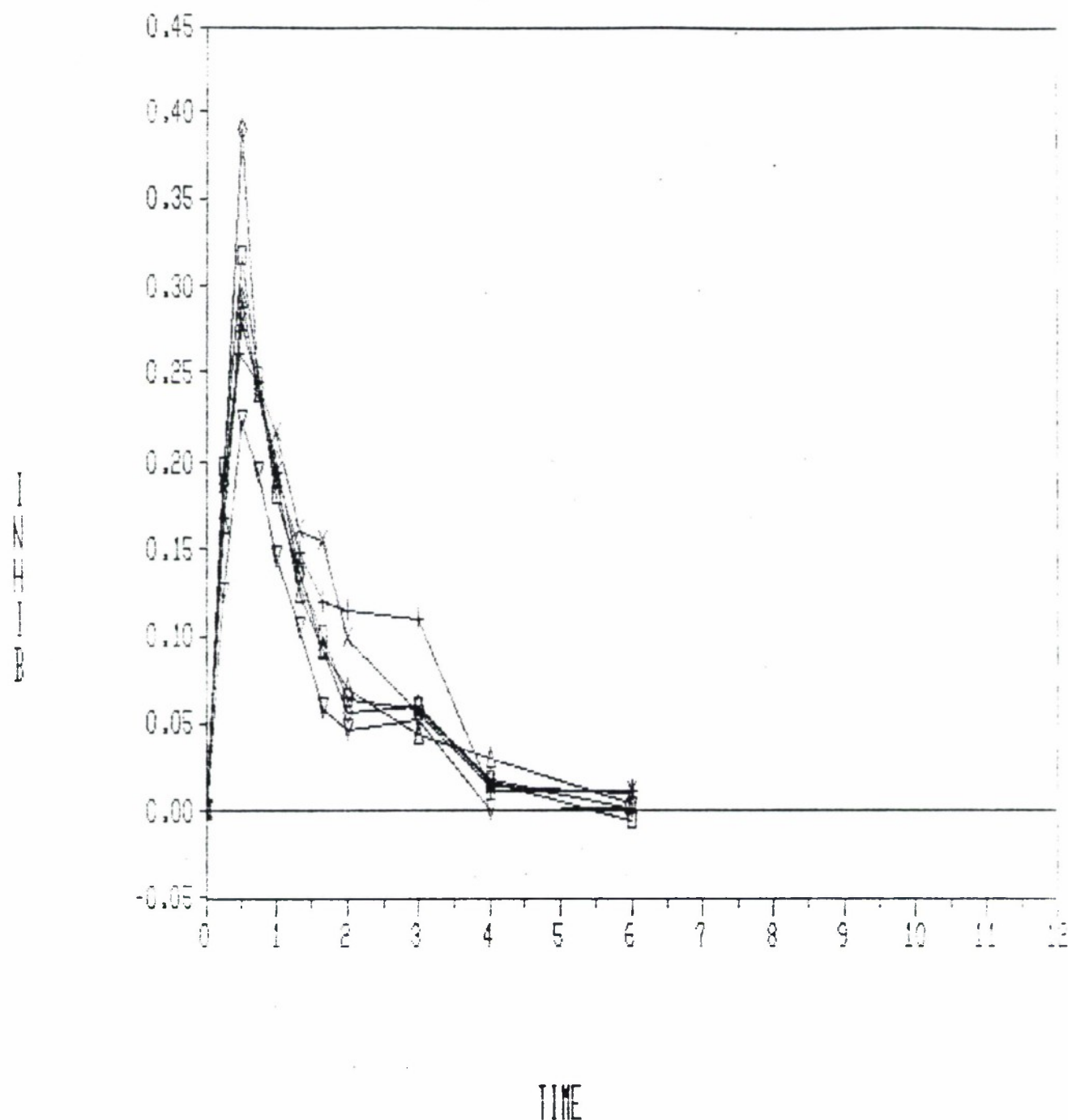
Time in hours after dosing
 Subjects 7 - 12: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after intravenous administration of drug

Figure 4b



Time in hours after dosing
 Subjects 7 - 12: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after oral administration of drug

Figure 4c



◇ 13
△ 17

□ 14
▽ 18

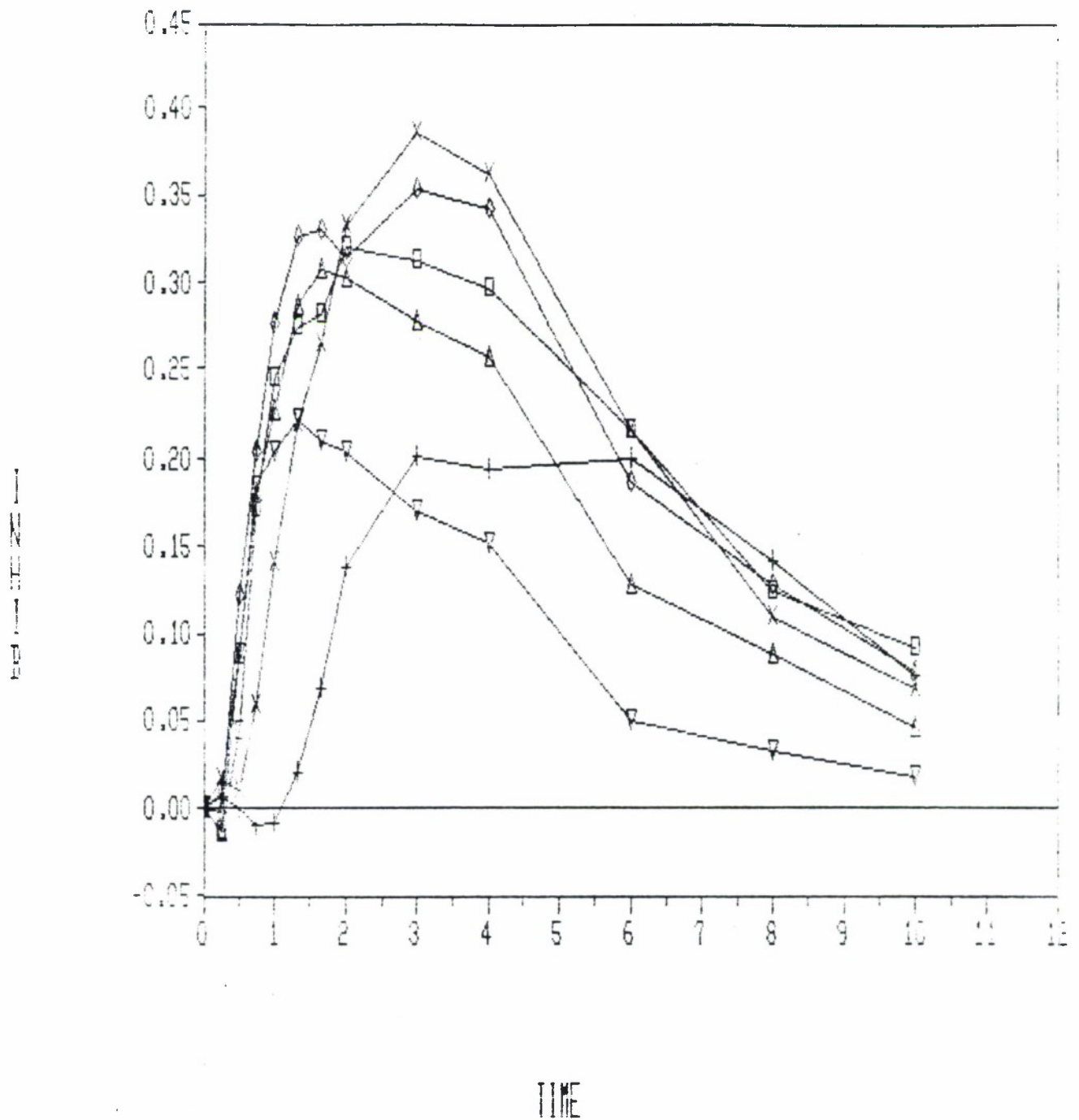
× 15

+ 16

Time in hours after dosing

Subjects 13 - 18: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after intravenous administration of drug

Figure 4d

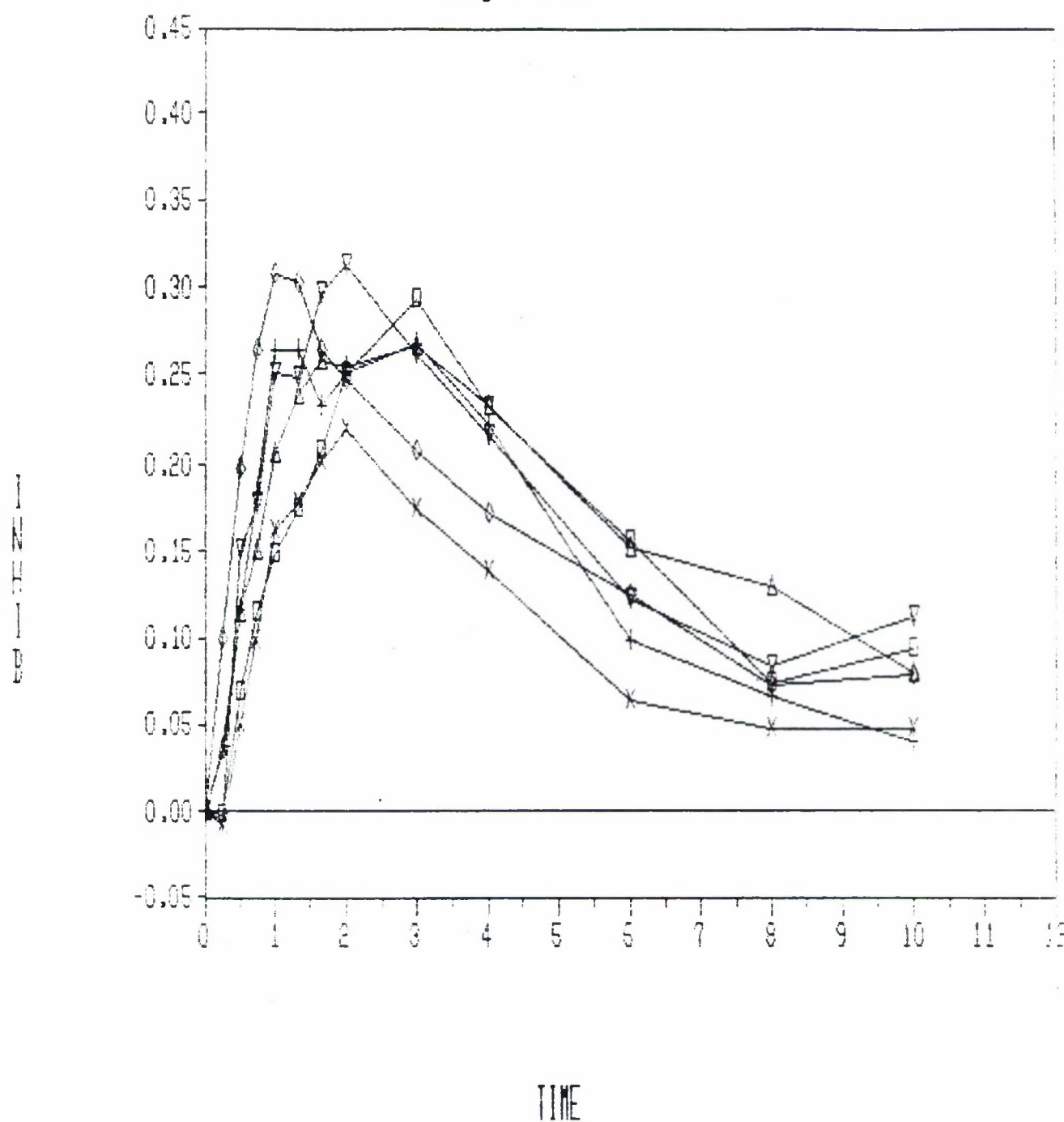


♦ 13 ◻ 14 × 15 + 16
 Δ 17 ▽ 18

Time in hours after dosing

Subjects 13 - 18: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after oral administration of drug

Figure 4e



♦ 19
△ 23

□ 20
▽ 24

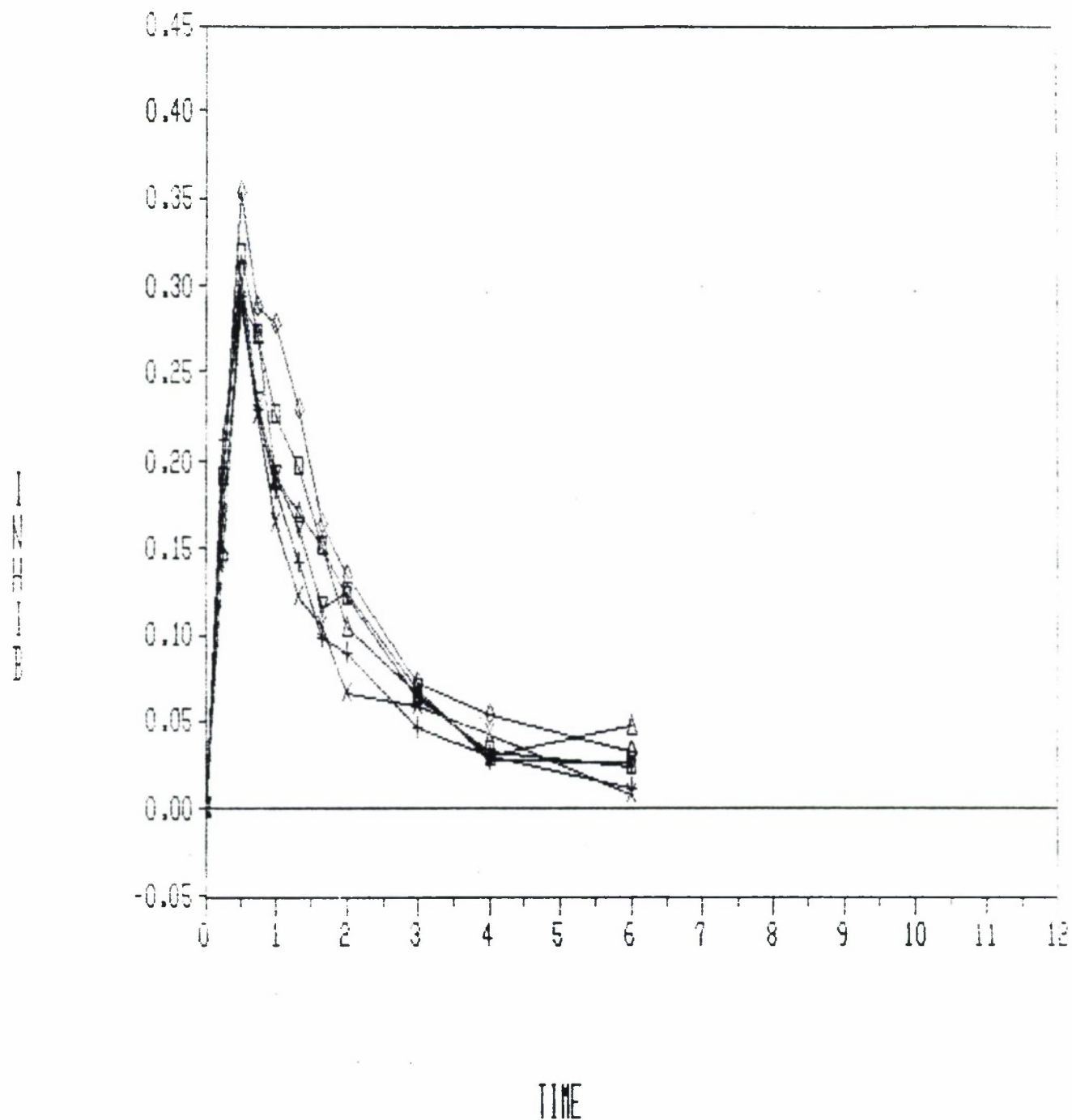
× 21

+ 22

Time in hours after dosing

Subjects 19 - 24: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after intravenous administration of drug

Figure 4f



♦ 19
△ 23

□ 20
▽ 24

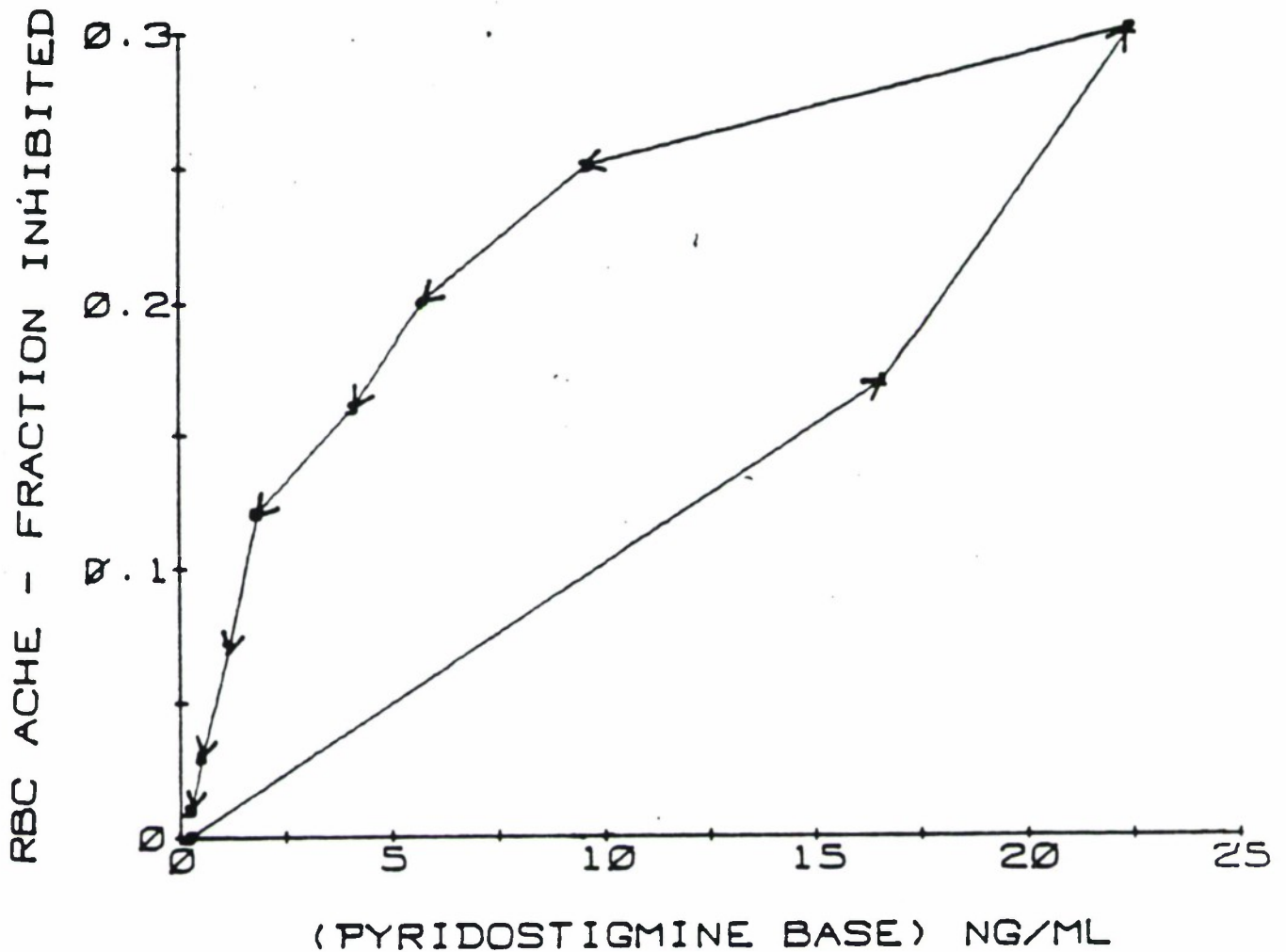
× 21

+ 22

Time in hours after dosing

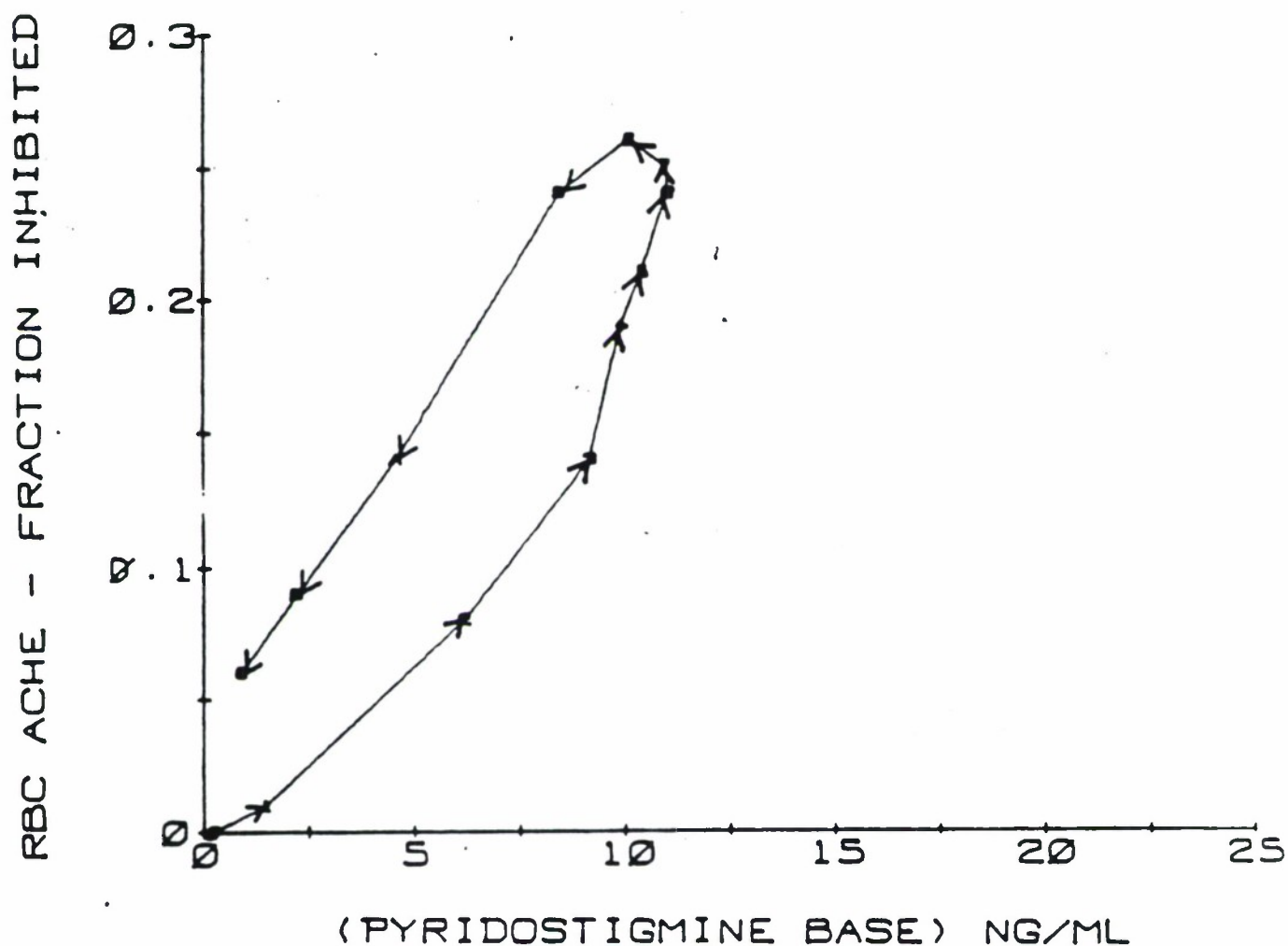
Subjects 19 - 24: Fractional inhibition of erythrocyte acetylcholinesterase at each sampling time after oral administration of drug

Figure 5a



Fractional inhibition of erythrocyte acetylcholinesterase after an intravenous dose of pyridostigmine plotted against the plasma concentration of pyridostigmine base in nanograms per milliliter. At each sampling time after dosing the mean fractional inhibition is plotted against the mean pyridostigmine concentration. The data points are connected in sequence beginning with the baseline sample.

Figure 5b



Fractional inhibition of erythrocyte acetylcholinesterase after an oral dose of pyridostigmine plotted against the plasma concentration of pyridostigmine base in nanograms per milliliter. At each sampling time after dosing the mean fractional inhibition is plotted against the mean pyridostigmine concentration. The data points are connected in sequence beginning with the baseline sample.

APPENDIX A

DETERMINATIONS OF PYRIDOSTIGMINE DOSE ADMINISTERED

The amount of pyridostigmine in each intravenous and oral dose was determined. Syringes containing the intravenous pyridostigmine solution were intentionally overfilled by the pharmacy so that a small aliquot of each solution could be expelled and saved for pyridostigmine assay in the process of preparing the correct volume of solution to administer. Just before the syringe containing the intravenous pyridostigmine was placed in the electrical infusion pump for infusion, it was weighed on a Mettler balance. The infusion was administered, and upon removing the syringe from the pump it was promptly weighed again on the Mettler balance. The specific gravity of the pyridostigmine solution was determined by delivering exactly 5 ml of the solution using a Rainin pipette into a pre-weighed beaker, and dividing by 5 to determine the weight of the solution per milliliter.

A similar procedure was followed for oral dosing. The appropriate volume of syrup was drawn up into the syringe and weighed on a Mettler balance. The dose was administered by expelling the contents of the syringe onto the volunteer's tongue, and the syringe was promptly weighed again. The specific gravity of the syrup was determined by placing exactly 10 ml of syrup in a pre-weighed volumetric flask, weighing the flask with its syrup contents, subtracting to find the weight of the syrup, and dividing that weight by 10 to determine the weight of syrup per milliliter.

The weights of the syringe before and after dosing, the weight of the dose, the specific gravity of the solution, the concentration of pyridostigmine by assay after the solution, and the total dose administered, is provided in the following table:

Subject	Route	Pre-Dose Syringe Weight (grams)	Post-Dose Syringe Weight (grams)	Weight Administered Drug (grams)	Specific Gravity (g/ml)	Volume Administered (uL)	Concent. of Administered Drug (ug/ml)	Dose of Drug Administered (mg base)
7	IV	42.74206	22.68077	20.06129	1.00225	20016.25	45	0.90073
8	IV	42.54756	22.48720	20.06036	1.00225	20015.33	43	0.86066
9	IV	42.74748	22.65576	20.09172	1.00225	20046.62	46	0.92214
10	IV	42.44876	22.43366	20.01510	1.00225	19970.17	46	0.91863
11	IV	42.35694	22.34901	20.00793	1.00225	19963.01	47	0.93826
12	IV	42.55140	22.48629	20.06511	1.00225	20020.06	49	0.98098
13	IV	41.77491	21.83540	19.93951	1.00225	19894.75	46	0.91516
14	IV	41.94086	21.84021	20.10065	1.00225	20055.53	48	0.96267
15	IV	42.46026	22.27323	20.18703	1.00225	20141.71	43	0.86609
16	IV	43.42423	23.16032	20.26391	1.00225	20218.42	47	0.95027
17	IV	42.69	22.68	20.01	1.00225	19965.08	42	0.83853
18	IV	42.43	22.47	19.96	1.00225	19915.19	39	0.77669
19	IV	42.73	22.95	19.78	1.00225	19735.59	47	0.92757
20	IV	42.36	22.38	19.98	1.00225	19935.15	47	0.93695
21	IV	41.82	21.77	20.05	1.00225	20004.99	42	0.84021
22	IV	41.41	21.58	19.83	1.00225	19785.48	46	0.91013
23	IV	43.15	23.13	20.02	1.00225	19975.06	48	0.95880
24	IV	43.16	23.04	20.12	1.00225	20074.83	41	0.82307
								Mean
								Std. Dev.
7	Oral	7.62439	5.99580	1.62859	1.23235	1321.53	7563.33	9.99515
8	Oral	7.62874	5.98388	1.64486	1.23235	1334.73	7563.33	10.09500
9	Oral	7.63517	5.95228	1.68289	1.23235	1365.59	7563.33	10.32841
10	Oral	7.62954	5.95975	1.66979	1.23235	1354.96	7563.33	10.24801
11	Oral	7.61223	5.94095	1.67128	1.23235	1356.17	7563.33	10.25715
12	Oral	7.65615	5.97785	1.67830	1.23235	1361.87	7563.33	10.30024
13	Oral	7.65328	5.97348	1.67980	1.23235	1363.08	7563.33	10.30944
14	Oral	7.60178	5.94663	1.65515	1.23235	1343.08	7563.33	10.15816
15	Oral	7.60	5.94	1.66	1.23235	1347.02	7563.33	10.18792
16	Oral	7.54	5.90	1.64	1.23235	1330.79	7563.33	10.06518
17	Oral	7.63947	5.95118	1.68829	1.23235	1369.97	7563.33	10.36155
18	Oral	7.63564	5.94243	1.69321	1.23235	1373.96	7563.33	10.39174
19	Oral	7.63020	5.95638	1.67382	1.23235	1358.23	7563.33	10.27274
20	Oral	7.63334	5.95644	1.67690	1.23235	1360.73	7563.33	10.29164
21	Oral	7.65638	5.96912	1.68726	1.23235	1369.14	7563.33	10.35523
22	Oral	7.65638	5.97471	1.68167	1.23235	1364.60	7563.33	10.32092
23	Oral	7.68977	5.99311	1.69666	1.23235	1376.76	7563.33	10.41292
24	Oral	7.63559	5.96846	1.66713	1.23235	1352.80	7563.33	10.23168
								Mean
								Std. Dev.

The weights reported above were obtained using a Mettler analytical balance, except where the weights are reported only to the nearest hundredth gram. In those case, a table top Mettler balance was used because the analytical Mettler balance was not functional.

It should be noted that the mean dose of drug administered intravenously, expressed as milligrams of base, was 0.90153 mg, and corresponds to a dose of 1.3 mg pyridostigmine bromide. For the oral dose, the mean pyridostigmine base of 10.25462 mg administered corresponds to a dose of 14.8 mg pyridostigmine bromide.

APPENDIX B

PROCEDURAL TIMETABLE

		DAY NUMBER						
	Screening*	1	2	3	4	5	6	13**
Medical history	X							
Physical examination	X							
CBC with differential	X	X		X			X	
Reticulocyte count		X		X			X	
SMA-6	X	X		X			X	
SMA-12	X	X		X			X	
LDH	X	X		X			X	
CPK***	X	X		X			X	
Chest x-ray (within 6 months)	X							
Electrocardiogram	X			X			X	
Urinalysis	X	X		X			X	
Red blood cell acetylcholinesterase		X	X	X		X	X	
Pyridostigmine levels			X	X		X	X	
Drug administration			X			X		
Discharge from hospital							X	

* Screening is conducted within two weeks of the subject's entry into the hospital.

** If the subject's clinical labs on Day 6 are abnormal, he will be invited to return for follow-up clinical testing on Day 13 and weekly thereafter until tests become normal or an alternative explanation is determined.

*** CPK (creatine phosphokinase) is equivalent to creatine kinase (CK), the nomenclature used elsewhere in this report except here in Appendix B.

STUDY FLOW CHART - DOSE-RANGING PHASE

<u>DAY</u>	<u>HOURL</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
1	-21	11:00 AM	Subjects admitted to Unit Sign Consent Form Blood: CBC with differential Reticulocyte count SMA-6 SMA-12 LDH CPK Red blood cell acetylcholinesterase (RBC AChE) EKG Urinalysis
2	-8	12:00 MN	NPO No smoking
	-1	7:00 AM	Insert heparin lock for blood sampling
	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip, coordination testing (clinical examination) <u>ADMINISTER TEST DRUG</u> Pyridostigmine 0.66 mg IV over 30 minutes by infusion pump
	0.08	8:05 AM	Blood: Pyridostigmine level
	0.16	8:10 AM	Blood: Pyridostigmine level
	0.25	8:15 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	0.33	8:20 AM	Blood: Pyridostigmine level

(continued)

<u>DAY</u>	<u>HOUR</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
2	0.42	8:25 AM	Blood: Pyridostigmine level
	0.50	8:30 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip, coordination testing (clinical examination)
	0.58	8:35 AM	Blood: Pyridostigmine level
	0.66	8:40 AM	Blood: Pyridostigmine level
	0.75	8:45 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	0.83	8:50 AM	Blood: Pyridostigmine level
	0.92	8:55 AM	Blood: Pyridostigmine level
	1.0	9:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	1.33	9:20 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	1.66	9:40 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	2.00	10:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	2.5	10:30 AM	Blood: Pyridostigmine level

(continued)

<u>DAY</u>	<u>HOURL</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
2	3.0	11:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	3.5	11:30 AM	Blood: Pyridostigmine level
	4.0	12:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	5.0	1:00 PM	Blood: Pyridostigmine level
	6.0	2:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	7.0	3:00 PM	Blood: Pyridostigmine level
	8.0	4:00 PM	Blood: Pyridostigmine level and CPK
	10.0	6:00 PM	Blood: Pyridostigmine level
	12.0	8:00 PM	Blood: Pyridostigmine level
3	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level CBC with differential Reticulocyte Count SMA-6 SMA-12 LDH CPK Urinalysis EKG Pulse rate, hand grip Heparin lock may be discontinued if the patient desires

(continued)

<u>DAY</u>	<u>HOURL</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
4			No procedures scheduled
5	-8	12:00 MN	NPO No smoking
	-1	7:00 AM	Insert heparin lock for blood sampling
	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip <u>ADMINISTER TEST DRUG</u> Pyridostigmine 20 mg syrup orally
	0.25	8:15 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	0.50	8:30 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	0.75	8:45 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	1.0	9:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	1.33	9:20 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	1.66	9:40 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	2.0	10:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	2.5	10:30 AM	Blood: Pyridostigmine level

(continued)

<u>DAY</u>	<u>HOURL</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
5	3.0	11:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	3.5	11:30 AM	Blood: Pyridostigmine level
	4.0	12:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	5.0	1:00 PM	Blood: Pyridostigmine level
	6.0	2:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	7.0	3:00 PM	Blood: Pyridostigmine level
	8.0	4:00 PM	Blood: Pyridostigmine level and CPK
	10.0	6:00 PM	Blood: Pyridostigmine level
	12.0	8:00 PM	Blood: Pyridostigmine level
6	0	8:00 AM	Blood: CBC with differential Reticulocyte count SMA-6 SMA-12 LDH CPK RBC AChE level Pyridostigmine level Pulse rate, hand grip, coordination testing (clinical examination) EKG Urinalysis Discharge after breakfast

NOTE: There will be no timed urine collections for this protocol.

STUDY FLOW CHART - BIOAVAILABILITY PHASE

<u>DAY</u>	<u>HOURL</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
1	-21	11:00 AM	Subjects admitted to Unit Sign Consent Form Blood: CBC with differential Reticulocyte count SMA-6 SMA-12 LDH CPK Red blood cell acetylcholinesterase (RBC AChE) EKG Urinalysis
2	-8	12:00 MN	NPO No smoking
	-1	7:00 AM	Insert heparin lock for blood sampling
	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip, coordination testing (clinical examination) <u>ADMINISTER TEST DRUG</u> Pyridostigmine intravenous solution Dose will be based upon the data obtained in the Dose Ranging Phase. The doses administered will be such that RBC AChE inhibition will be between 20% and 40%.
	0.08	8:05 AM	Blood: Pyridostigmine level
	0.16	8.10 AM	Blood: Pyridostigmine level
	0.25	8:15 AM	Blood: Pyridostigmine level
	0.33	8:20 AM	Blood: Pyridostigmine level
	0.42	8:25 AM	Blood: Pyridostigmine level

(continued)

<u>DAY</u>	<u>HOUR</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
2	0.50	8:30 AM	Blood: Pyridostigmine level Hand grip, coordination testing (clinical examination)
	0.58	8:35 AM	Blood: Pyridostigmine level
	0.66	8:40 AM	Blood: Pyridostigmine level
	0.75	8:45 AM	Blood: Pyridostigmine level
	0.83	8:50 AM	Blood: Pyridostigmine level
	0.92	8:55 AM	Blood: Pyridostigmine level
	1.0	9:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	1.33	9:20 AM	Blood: Pyridostigmine level
	1.66	9:40 AM	Blood: Pyridostigmine level
	2.0	10:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	2.5	10:30 AM	Blood: Pyridostigmine level
	3.0	11:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	3.5	11:30 AM	Blood: Pyridostigmine level
	4.0	12:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	5.0	1:00 PM	Blood: Pyridostigmine level
	6.0	2:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	7.0	3:00 PM	Blood: Pyridostigmine level
	8.0	4:00 PM	Blood: Pyridostigmine level and CPK

(continued)

<u>DAY</u>	<u>HOUR</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
2	10.0	6:00 PM	Blood: Pyridostigmine level
	12.0	8:00 PM	Blood: Pyridostigmine level
3	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level, CBC with differential Reticulocyte count SMA-6 SMA-12 LDH CPK Pulse rate, hand grip EKG Urinalysis Heparin lock may be discontinued if the patient desires.
4			NO procedures scheduled
5	-8	12:00 MN	NPO No smoking
	-1	7:00 AM	Insert heparin lock for blood sampling
5	0	8:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip <u>ADMINISTER TEST DRUG</u> Pyridostigmine syrup
	0.25	8:15 AM	Blood: Pyridostigmine level
	0.50	8:30 AM	Blood: Pyridostigmine level Hand grip
	0.75	8:45 AM	Blood: Pyridostigmine level
	1.0	9:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	1.33	9:20 AM	Blood: Pyridostigmine level

(continued)

<u>DAY</u>	<u>HOUR</u>	<u>APPROXIMATE TIME</u>	<u>PROCEDURE</u>
	1.66	9:40 AM	Blood: Pyridostigmine level
	2.0	10:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	2.5	10:30 AM	Blood: Pyridostigmine level
	3.0	11:00 AM	Blood: Pyridostigmine level RBC AChE level Pulse rate
	3.5	11:30 AM	Blood: Pyridostigmine level
	4.0	12:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	5.0	1:00 PM	Blood: Pyridostigmine level
	6.0	2:00 PM	Blood: Pyridostigmine level RBC AChE level Pulse rate, hand grip
	7.0	3:00 PM	Blood: Pyridostigmine level
	8.0	4:00 PM	Blood: Pyridostigmine level and CPK
	10.0	6.00 PM	Blood: Pyridostigmine level
	12.0	8:00 PM	Blood: Pyridostigmine level
6	0	8:00 AM	Blood: CBC with differential Reticulocyte count SMA-6 SMA-12 LDH CPK RBC AChE level Pyridostigmine level Pulse rate, hand grip, coordination testing (clinical examination) EKG Urinalysis Discharge after breakfast

NOTE: There will be no timed urine collections for this protocol.

APPENDIX C

CLINICAL LABORATORY NORMAL VALUES

The ranges of these values have been determined and are utilized by the Department of Laboratory Medicine of The Johns Hopkins Hospital.

<u>Serum Chemistry</u>	<u>Normal Limits</u>		<u>Units</u>
<u>Tests</u>	<u>Lower</u>	<u>Upper</u>	
Sodium	135	148	mEq/l
Potassium	3.5	5.0	mEq/l
Chloride	96	109	mEq/l
Carbon dioxide	24	30	mEq/l
Serum urea nitrogen	12	25	mg/dl
Creatinine	0.4	1.5	mg/dl
Glucose	70	115	mg/dl
Calcium	9.0	11.0	mg/dl
Total bilirubin	0.3	1.2	mg/dl
Direct bilirubin	0.1	0.4	mg/dl
Total protein	6.0	8.5	g/dl
Albumin	3.2	5.3	g/dl
Aspartate aminotransferase	0	35	IU/l
Alanine aminotransferase	0	30	IU/l
Alkaline phosphatase	0	95	IU/l
Phosphate, inorganic	3.0	4.5	mg/dl
Lactic dehydrogenase	0	200	IU/l
Creatine kinase	0	160	IU/l
Uric Acid	4.2	8.8	mg/dl
Cholesterol	146	270	mg/dl

	<u>Normal Limits</u>		<u>Units</u>
	<u>Lower</u>	<u>Upper</u>	
<u>Hematology Tests</u>			
White blood cells	4,500	11,000	#/mm ³
Red blood cells	4.50	5.90	million/mm ³
Hemoglobin	13.9	16.3	g/dl
Hematocrit	41.0	53.0	%
Platelets	150	350	thousand/mm ³
Reticulocytes	0.5	1.5	%
White Blood Cell Differentials:			
Bands	2	6	%
Segmental Neutrophils	31	76	%
Lymphocytes	24	44	%
Monocytes	2	11	%
Eosinophils	1	4	%
Basophils	0	1	%

APPENDIX D

ASSAY OF ERYTHROCYTE ACETYLCHOLINESTERASE AT THE JOHNS HOPKINS UNIVERSITY DIVISION OF CLINICAL PHARMACOLOGY

The determination of erythrocyte acetylcholinesterase (AChE) follows the protocol established by the US Army Medical Research Institute for Chemical Defense for the determination of erythrocyte AChE.

Principle of Method, Chemicals, Equipment and Materials, Preparation of Reagents

The principles of the methods, the chemicals, materials, and equipment needed, the preparation of reagents and standards are detailed in the Standard Operating Procedure (SOP) of 18 June 1985 of the Analytical Chemistry Branch, USAMR, ICD, Aberdeen Proving Ground, Maryland 21010. These are followed exactly except for preparation of the stock glutathione solution, page 3, number 6 under A. Reagents. The typographical error is corrected and 1.844 g of glutathione, reduced form, (GSH) are dissolved in a total volume of 100ml of EDTA diluent.

Collection and Preparation of Specimen for Sampling

Blood is collected into 3 ml purple topped Vacutainer^R (EDTA) through a catheter inserted into an arm vein. After the sample is drawn, it is mixed and brought promptly to the lab at room temperature. One and one half ml of the blood is centrifuged for 2 minutes at 15,000 RPM in an Eppendorf model 5414 centrifuge. After centrifugation all plasma is removed from

the top of the packed erythrocytes with a Pasteur pipet. The erythrocytes are then picked up in a clean Pasteur pipet, starting from the bottom of the centrifuge tube, avoiding drawing air after all the cells have been pipetted. The packed cells are transferred to a 0.5 ml sample cup and are ready for AChE analyses. Sample preparation time is kept to 3 minutes.

Preparation of Standards

Standards are prepared according to the SOP of the ICD.

Preparation of AChE Control Material

A quality control enzyme standard is used to measure assay precision. The enzyme used is electric eel AChE which is diluted in a large volume to a specific activity and frozen in aliquots. An aliquot is used each day the assay is performed. Electric eel samples were assayed in accordance with ICD SOP. See below for specific details.

Analysis Start-Up

ICD SOP is followed. The heating circulator is turned on. We allow temperature to reach 37 degrees C and verify constancy periodically.

Proportioning Pump

ICD SOP is followed. Water with Brij 35 precedes the reagents. A good bubble pattern is verified.

Colorimeter and Recorder

ICD SOP is followed. Lamp warmup is at least 10 minutes. Once reagents are running, the recorder is zeroed for no signal and full scale. Speed is set to 1.0 cm/min.

Sampler

ICD SOP is followed. Proper operation of sampler is verified prior to running any samples.

Analyses

Recorder baseline is set to zero.

Manifold has been modified so that the substrate blank side pumps saline continuously. Erythrocytes enter only one side and one photo cell. At the end of the day, a substrate blank is run by placing the substrate line into saline and measuring the activity of the erythrocytes without a substrate. ICD SOP is followed.

Incubation time is measured. The length of time it takes erythrocytes to travel from the point where substrate is added to the sample stream until exit from the dialyzer is defined as the incubation time.

GSH standards and electric eel AChE are assayed first. A 60 micromoles/ml (u moles/ml) GSH standard is assayed followed by 15, 30, and 45 u moles/ml GSH standards, and a 1:1 dilution of the electric eel quality control. Machine sensitivity is adjusted using the STD CAL knob so that the 60 u moles/ml standard reads 80 to 90 on the recorder scale. Two standard curves and a minimum 3 electric eel samples are assayed prior to assay of erythrocyte samples. Erythrocyte samples are separated by at least two saline cups. Machine performance is standardized periodically throughout the day by running standard curves and electric eel samples. Gain is decreased if the 60 u moles/ml GSH rises above 90. Where possible, standards are assayed hourly and

erythrocyte samples measured in duplicate.

Shut Down SOP

ICD is followed. Care is taken to dry the tubes and to insure that they are in a relaxed position.

Data Reduction

AChE activity is determined as follows:

The concentration of each GSH standard is divided by the peak height of the deflection produced. This value is then divided by the time of incubation in minutes to produce a factor of μ moles/ml/min/chart unit. The individual factors from each standard in the curve are averaged. The average factor, μ moles/ml/min/chart unit, is used to convert the deflection produced by samples to AChE activity, μ moles/ml/min.

ASSAY PERFORMANCE AT JOHNS HOPKINS HOSPITAL

Quality Control

A standard solution of electric eel acetylcholinesterase is measured several times on the days that assays are performed.

The current batch of JHH electric eel was prepared on 14 October 1985 using Sigma Co, Type VI-S Cholinesterase, Acetyl (catalog #C3389) from electric eel, Lot #83F8100. One 10,000 unit vial was diluted in Tris buffer containing 1% bovine serum albumin. The dilution target was such that a one to one dilution of the solution should contain 15.0 μ moles/ml/min of cholinesterase activity.

After the dilution, aliquotting and freezing of the cholinesterase solution was performed, it was discovered that the

colorimeter was not functioning correctly and that the GSH standards were in error. New standards were made; the colorimeter was repaired. The instrument was calibrated with GSH standards and the Aberdeen quality control standard. The latter's activity was 7.46 u moles/ml/min, within the range at ICD, Aberdeen.

The assay was used on 13 different days. On each day an aliquot of the electric eel quality control standard was thawed and assayed several times. The overall statistics of 127 samples from the 13 aliquots show mean activity 9.88 u moles/ml/min with a standard deviation of 0.27 u moles/ml/min. The coefficient of variation is 2.7%. Looking only at the means of the assays in a single day, the activity of the quality control is 9.91 ± 0.23 u moles/ml/min (C.V. = 2.3%).

Precision

Blood samples were drawn from 6 study subjects prior to drug administration. Each sample was assayed on several occasions. The results are tabulated in the Table.

The intra-assay coefficient of variation ranged from 0.5 to 3.5%, with a mean of 2.5%. Day to day variations in the measurement of a subject's drug free erythrocyte AChE ranged from 0.14 to 0.67 u moles/ml/min or 1.08 to 5.48% of the value on a single day. This variation is about twice the intra-assay variation and suggests that either the inter-assay variation is greater than that of the intra-assay and/or the activity of erythrocyte AChE drawn from a single subject on different days varies to a small degree.

With a coefficient of variation of 2.5% in the assay, inhibition of enzyme activity of 5% or more probably represents real inhibition by pyridostigmine, not random variation due to the assay.

TABLE - APPENDIX D

ERYTHROCYTE ACETYLCHOLINESTERASE ACTIVITY IN 6 NORMAL VOLUNTEERS

Intra-Assay and Inter-Assay Results

Subject	Day	n	AChE u moles/ml/min (\pm S.D.)	C.V. %	b-a u moles/ml/min	(b-a)/b %
A	a	7	12.90 \pm 0.31	2.4	0.14	1.08
	b	9	13.04 \pm 0.31	2.4		
B	a	10	13.82 \pm 0.37	2.7	0.66	4.78
	b	8	14.48 \pm 0.55	3.8		
C	a	8	12.59 \pm 0.36	2.9	0.69	5.48
	b	8	13.28 \pm 0.31	2.3		
D	a	4	13.20 \pm 0.52	3.9	0.67	5.08
	b	5	13.87 \pm 0.07	0.5		
E	a	4	13.35 \pm 0.43	3.2	0.51	3.82
	b	6	13.86 \pm 0.33	2.4		
F	a	4	14.26 \pm 0.36	2.5	0.60	4.21
	b	6	14.86 \pm 0.20	1.3		

Form C (Revised 4/84)
J.H.U.M.S.

CLINICAL INVESTIGATION CONSENT FORM

The Johns Hopkins Medical Institutions

Title of Research Project:

BIOAVAILABILITY OF ORAL PYRIDOSTIGMINE AND INHIBITION
OF ACETYLCHOLINESTERASE BY ORAL AND INTRAVENOUS
PYRIDOSTIGMINE

Patient I.D. Plate

Explanation of Research Project to Subject:

You are invited to participate in a study of an approved and marketed drug, pyridostigmine. This drug is currently in use for treating patients with a disease called myasthenia gravis. The drug, based on studies in animals, may also be an effective pre-treatment for accidental poisoning with certain insecticides which work in ways similar to nerve gases. This study is designed to see how much of the drug gets into the blood stream when given by mouth and how effective the levels are in changing a blood test that may relate to the degree of protection from poisoning.

If you agree to join this study, you will be hospitalized for five days. During the course of the hospitalization you will have a number of blood samples drawn by means of a "heparin lock" which allows us to take repeated blood samples without sticking a new needle into your vein each time. The total blood taken will be about one pint, which is the amount taken if you donated blood at a blood bank. You should not donate blood for six to eight weeks after the conclusion of the study.

On the second day, after the first blood sample is taken, you will be given the drug pyridostigmine, either in syrup form or into your vein. On the fifth day, you will be given pyridostigmine in the manner not previously given (i.e., syrup or into the vein). Whether you get the syrup or dose by vein first will be determined "randomly" in a process like flipping a coin.

We believe that the risks of participation in this study are small. Pyridostigmine is not an experimental drug. The dose of the drug you will receive is much smaller than the dose usually used in treating patients. In a study similar to this one where doses about three times larger than the ones you will receive were used, the only side effects noted were temporary fatigue, muscle twitching, and gastric distress. Patients who take more than 20 times as much of the drug each day than you will receive in this study sometimes develop nausea, vomiting, diarrhea, abdominal cramps, and increased body secretions. Because the dose you will receive is so much smaller than what doctors use in patients, it is not likely that you will develop these symptoms. Treatment is available if any such symptoms occur and become severe.

You are under no obligation to participate in this project. Should you decide not to participate or should you decide to withdraw during the course of the project, your future medical care at Hopkins will not be affected. Benefits to you for participation in this study are primarily financial, but another potential asset is the comprehensive evaluation which accompanies this project, the records of which will be available in the future. You will be paid by check for whatever proportion of the study you complete. Successful completion of the entire study will pay \$340. You will be paid by check at the time you leave the hospital.

Expenses for medical treatment to treat any injury that is directly a result of your participation in accordance with this protocol will be provided by the U.S. Army. The medical treatment provided might include, if necessary, laboratory tests, x-rays, and other procedures used in diagnosis and treatment. No other compensation for injury is offered.

THIS CONSENT FORM CONTINUES ON THE REVERSE SIDE

If you sign this form, you are willing to join the research project described on the other side of this page. Your doctors did explain the other kinds of treatment that are available to you and to others. You should ask any questions you have about this research study. You may ask questions in the future if you do not understand something that is being done.


The records from this research study will not be given to anyone who is not helping on this study unless you agree to have the records given out. If the study uses a drug that is under the jurisdiction of the Food and Drug Administration (FDA), the FDA government officials may look at the relevant part of your medical records as part of their job to review new drug studies.

If you want to talk to anyone about this research study because you think you have not been treated fairly or you think you have been hurt by joining the study, you should call Dr. Brent G. Petty (Principal Investigator) at 955 - 8181, or call the Office of the Joint Committee on Clinical Investigation at 955-3008. Either the investigator or the people in the Committee office will help to find medical care for the injury you feel you have suffered. You should understand that The Johns Hopkins University, The Johns Hopkins Hospital, and the Federal Government do not have any program to provide compensation for you if you experience injury or other bad effects which are not the fault of the investigators.

You may withdraw from the research study at any time. Even if you do not want to join the study, or if you withdraw from it, you will still have the same quality of medical care available to you at Johns Hopkins.

If you agree to join this study, please sign your name below.

NOT VALID WITHOUT THE
COMMITTEE STAMP OF
CERTIFICATION



VOID ONE YEAR FROM ABOVE DATE
RPN No. 85-06-20-03

Subject's signature
(Including children, when applicable)

Signature of Parent or Guardian (when applicable)

Witness to Consent Procedures*

Signature of Investigator

Date

*Optional unless subject is illiterate, or unable to sign.

NOTE: Signed copies of this consent form must be a) retained on file by the Principal Investigator;
b) deposited in the patient's medical record; and c) given to the patient.

CLINICAL INVESTIGATION CONSENT FORM
The Johns Hopkins Medical Institutions

Title of Research Project: Bioavailability of Oral
Pyridostigmine and Inhibition of
Acetylcholinesterase by Oral and
Intravenous Pyridostigmine

Patient I.D. Plate

Explanation of Research Project to Subject:

You are invited to participate in a study of an approved and marketed drug, pyridostigmine. Pyridostigmine is a medicine that has been prescribed for patients, using daily doses for months or years, for a period of over 20 years. This drug is used for treating patients with a disease called myasthenia gravis. The drug, based on studies in animals, may also be effective pre-treatment for accidental poisoning with certain insecticides which work in ways similar to nerve gases. This use of the drug is considered investigational by the Food and Drug Administration. This study is designed to see how high the drug level is in the blood stream when given by mouth or into your vein and how effective the levels are in changing a blood test that may relate to the degree of protection from poisoning.

If you agree to join this study, you will be hospitalized for five days. During the course of the hospitalization you will have a number of blood samples drawn by means of a "heparin lock" which allows us to take repeated blood samples without sticking a new needle into your vein each time. The total blood taken will be about one pint which is the amount taken if you donated blood at a blood bank. You should not donate blood for six to eight weeks after the conclusion of the study.

On the second day, after the first blood sample, you will be given the drug pyridostigmine, either in syrup form or into your vein. On the fifth day, you will be given pyridostigmine in the manner not previously given (i.e., syrup or into the vein.) Whether you get the syrup or intravenous dose first will be determined "randomly" in a process like flipping a coin.

We believe that the risks of participation in this study are small. Pyridostigmine is considered an experimental drug in this project because of the new use for which it is intended. The dose of the drug you will receive is much smaller than the dose usually used in treating patients. In a study similar to this one where doses about three times larger than the ones you will receive were used, the only side effects noted were temporary fatigue, muscle twitching, and gastric distress. Patients who take more than 20 times as much of the drug each day than you will in this study sometimes develop nausea, vomiting, diarrhea, abdominal cramps, and increased body secretions. Because the dose you will receive is so much smaller than what doctors use in patients, it is not likely that you will develop these symptoms. Treatment is available if any such symptoms occur and become severe.

Recently, a possible new toxicity in rats was discovered which may be related to the drug. The rats were given pyridostigmine in a higher dosage than the one planned for this study. A change in the muscle tissues in the area where the nerves and muscles meet was seen using the electron microscope. The significance of this finding is unknown, but it is generally accepted in the medical field that pyridostigmine is safe for man at the doses to be used in this study. Further testing in other animals is being done to see if this nerve-muscle effect occurs in animals other than the rat. Additional tests in rats are in progress to find out the dose at which the effect occurs and whether the tissue returns to normal when the pyridostigmine is stopped. If results of these tests become available during this study, you will be informed of them. Until these tests are completed, a small risk of developing these changes cannot be ruled out for participants in this study. However, all

THIS CONSENT FORM CONTINUES ON THE REVERSE SIDE

If you sign this form, you are willing to join the research project described on the other side of this page. Your doctors did explain the other kinds of treatment that are available to you and to others. You should ask any questions you have about this research study. You may ask questions in the future if you do not understand something that is being done.

The records from this research study will not be given to anyone who is not helping on this study unless you agree to have the records given out. Since the study uses a drug that is under the jurisdiction of the Food and Drug Administration (FDA), the FDA government officials may look at the relevant part of your medical records as part of their job to review new drug studies. Officials from the U.S. Army involved with drug development may also review the records for routine monitoring of the study.

If you want to talk to anyone about this research study because you think you have not been treated fairly or you think you have been hurt by joining the study, you should call Dr. Brent G. Petty (Principal Investigator) at x8181, or call the Office of the Joint Committee on Clinical Investigation at 955-3008. Either the investigator or the people in the Committee office will help to find medical care for the injury you feel you have suffered. You should understand that The Johns Hopkins University, The Johns Hopkins Hospital, and the Federal Government do not have any program to provide compensation for you if you experience injury or other bad effects which are not the fault of the investigator.

You may withdraw from the research study at any time. Even if you do not want to join the study, or if you withdraw from it, you will still have the same quality of medical care available to you at Johns Hopkins.

If you agree to join this study, please sign your name below.

NOT VALID WITHOUT THE
COMMITTEE STAMP OF
CERTIFICATION

Approved By The Joint Committee On Clinical Investigation

SEP 24 1985

VOID ONE YEAR FROM ABOVE DATE

RPN No. 85-06-20-03

Subject's signature

Witness to Consent Procedures

Signature of Investigator

Date

NOTE: Signed copies of this consent form must be a) retained on file by the Principal Investigator; b) deposited in the patient's medical record; and c) given to the patient.

experience with the clinical use of pyridostigmine in man over the past 20 years has not led to any reports of nerve-muscle difficulties attributed to or resulting from the use of this drug.

You are under no obligation to participate in this project. Should you decide not to participate or should you decide to withdraw during the course of the project, your future medical care at Hopkins will not be affected. Benefits to you for participation in this study are primarily financial, but another potential asset is the comprehensive evaluation which accompanies this project, the records of which will be available in the future. You will be paid by check for whatever proportion of the study you complete. Successful completion of the entire study will pay \$375. You will be paid by check at the time you leave the hospital.

Under Army regulation, you are authorized all necessary care which is the direct result of your participation in the research and in accordance with this protocol. The medical treatment provided might include, if necessary, laboratory tests, x-rays and other procedures used in diagnosis and treatment. No other compensation for injury is offered.

APPENDIX G

Publication Supported by this Contract

Kornhauser D, Petty B, Lin E, Schuster B, Pamplin C, Lietman P:
In vivo relationship of the plasma concentration of
pyridostigmine to the inhibition of red blood cell acetyl-
cholinesterase. III World Conference on Clinical Pharmacology
and Therapeutics, Stockholm, Sweden, July 27 - August 1, 1986.
(Abstract)

APPENDIX H

Personnel Receiving Contract Support

Paul S. Lietman, M.D., Ph.D., Principal Investigator

Brent G. Petty, M.D., Assistant Investigator

David M. Kornhauser, M.D., Investigator

Laura E. Rocco, R.N., M.S., Research Coordinator

Joan Baumgardner, R.N., Research Nurse

Sherry Sigelman, R.N., Research Nurse

Amina Woods, M.S., Laboratory Administrator

Evelyn Fleckenstein, Secretary

Michelle Janouris, Secretary

All of the personnel above are members of the:

Division of Clinical Pharmacology

Department of Medicine

The Johns Hopkins University School of Medicine

Baltimore, Maryland 21205

APPENDIX I
Distribution List

- 5 copies: Director, Walter Reed Army Institute of
Research
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Frederick, MD 21701-5009

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{C}{M} \frac{F}{L}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	10 OCT 85	Screening laboratory
—	17 OCT 85	History, Physical Exam
0	21 OCT 85	Admission
2	22 OCT 85	I.V.
5	25 OCT 85	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 01.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt G. Petty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R C F</u> F M L	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

17 Oct
Date of evaluation 10/17/85
dd mm yy
15 Nov
Date of birth 11/15/49
dd mm yy

Examiner

Brent G. Petty
Brent G. Petty
print name

Age 35 yrsSex MRace B

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1/2 p p d
Alcohol Use		✓	6 beers / wk
Recreational Drug Use		✓	Marijuana + heroin last 1-1 1/2 yrs
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	tobramycin study
Blood or plasma donor		✓	last ~ 1 year ago
Prior Surgery		✓	surgery @ zygomatic bone for Jan 1985
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use			Not asked
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R C F</u> <u>F M L</u>	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 17/01/85
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>36.7 C</u>	<u>82</u> min	<u>18</u> /min	<u>108/72</u>	<u>179.0</u>	<u>65.7</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		
Chest, lungs		✓	inspiratory rhachi ② base that clear with cough
Heart	✓		
Abdomen	✓		
Genitalia			N.D.
Rectal			N.D.
Extremities		✓	scar dorsum ② foot from childhood injury ~ 20 yrs. ago
Skin		✓	scratches both volar forearms from work
Neurologic	✓		

CHEST X-RAY

Date 10/17/85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R C F</u> <u>F M L</u>	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	220285	0900	0930	IV	N.A.

DOSAGE (total) .66 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	220285	0845	0845	B01: *	B47: 12.90
B02	0.08	"	0905	0905	B02: *	
B03	0.16	"	0910	0910	B03: 1.86	
B04, B48	0.25	"	0915	0915	B04: 5.17	B48: 11.53 11.53
B05	0.33	"	0920	0923	B05: 4.77	
B06	0.42	"	0925	0925	B06: 6.48	
B07, B49	0.50	"	0930	0930	B07: 6.88	B49: 10.73
B08	0.58	"	0935	0935	B08: 3.08	
B09	0.66	"	0940	0940	B09: 3.05	
B10, B50	0.75	"	0945	0945	B10: 1.86	B50: 10.79
B11	0.83	"	0950	0950	B11: *	
B12	0.92	"	0955	0955	B12: *	
B13, B51	1.0	"	1000	1000	B13: *	B51: 11.00
B14, B52	1.33	"	1020	1020	B14: *	B52: 11.89
B15, B53	1.66	"	1040	1040	B15: *	B53: 11.77
B16, B54	2.0	"	1100	1101	B16: *	B54: 12.06
B17	2.5	"	1130	1130	B17: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>C</u> <u>F</u> <u>F</u> <u>M</u> <u>L</u>	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	220285	0900	0930	IV	NA

DOSAGE (total) .66 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	R C F F M L	01	Pyridostigmine
			PROTOCOL
			DMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	220785	0900	0930	IV	NA

DOSAGE (total) .66 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	220785	0845	0845	#60	#41/45	#ck
	0.8	"	0905	0905			
	0.16	"	0910	0910			
	0.25	"	0915	0915	#60		
	0.33	"	0920	0920			
	0.42	"	0925	0925			
	0.50	"	0930	0930	#55	#46/49	#ck
	0.58	"	0935	0935			
	0.66	"	0940	0940			
	0.75	"	0945	0945	#58		
	0.83	"	0950	0950			
	0.92	"	0955	0955			
	1.0	"	1000	1000	#64	#46/51	
	1.33	"	1020	1020	#62		
	1.66	"	1040	1040	#56		
	2.0	"	1100	1100	#72	#44/52	
	2.5	"	1130	1130			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>C</u> <u>F</u> <u>F</u> <u>M</u> <u>L</u>	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Oct 85	0900	0930	IV	N+

DOSAGE (total) 1.66 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R C F</u> <u>F M L</u>	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Oct 85	0800	NA	PO	NA

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>ng/mL</u>	RBC ACHe <u>uM/ml/min</u>
B28, B59	0	25 Oct 85	not recorded	not recorded	B28: *	B59: <u>13.04</u> 3.04 ss
B29, B60	0.25	25 Oct 85	0815		B29: *	B60: <u>12.84</u> 11.1 ss
B30, B61	0.50	"	0830		B30: 4.97	B61: 11.07
B31, B62	0.75	"	0845		B31: 5.59	B62: 10.77
B32, B63	1.0	"	0900		B32: 8.8	B63: 10.03
B33, B64	1.33	"	0920		B33: 6.79	B64: 9.57
B34, B65	1.66	"	0940		B34: 8.14	B65: 9.59
B35, B66	2.0	"	1000		B35: 8.09	B66: 9.28
B36	2.5	"	1030		B36: 7.65	
B37, B67	3.0	"	1100		B37: 6.85	B67: 9.97
B38	3.5	"	1130		B38: 5.66	
B39, B68	4.0	"	1200		B39: 5.11	B68: 10.44
B40	5.0	"	1300		B40: 5.99	
B41, B69	6.0	"	1400		B41: 2.37	B69: 11.39
B42	7.0	"	1500		B42: *	
B43	8.0	"	1600		B43: *	B69A: N.D.
B44	10.0	"	1800		B44: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	R C E F M L	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	250185	0800	NA	PO	27

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{C}{M} \frac{F}{L}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	250785	0800	NA	PO	NA

DOSAGE (total) 20mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	250785	not recorded	not recorded	#60	#45/45	#ck
	0.25	"	0815	0815	#64		
	0.50	"	0830	0830	#64	#44/44	#ck
	0.75	"	0845	0845	#72		
	1.0	"	0900	0900	#64	#38/56	
	1.33	"	0920	0920	#84		
	1.66	"	0940	0940	#80		
	2.00	"	1000	1000	#92	#48/58	
	2.5	"	1030	1030			
	3.0	"	1100	1100	#84		
	3.5	"	1130	1130			
	4.0	"	1200	1200	#92	#45/53	
	5.0	"	1300	1300			
	6.0	"	1400	1400	#84	#44/49	
	7.0	"	1500	1500			
	8.0	"	1600	1600			
	10.0	"	1800	1800			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{array}{ccc} R & C & F \\ \hline F & M & L \end{array}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Oct 85	0800	NA	PO	NA

DOSAGE (total) 20 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R C F</u> <u>F M L</u>	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	<u>14 Oct 85</u> ddmmmyy	<u>21 Oct 85</u> ddmmmyy	<u>22 Oct 85</u> ddmmmyy	<u>23 Oct 85</u> ddmmmyy	<u>25 Oct 85</u> ddmmmyy
NA: 135-148 MEQ/L	146	142		142	
K: 3.5-5.0 MEQ/L	4.5	4.4		4.7	
CL: 96-109 MEQ/L	107	106		104	
CO2: 24-30 MEQ/L	28	28		30	
SUN: 12-25 MG/DL	12	15		11	
CREAT: 0.4-1.5 MG/DL	1.0	1.2		0.9	
GLU: 70-115 MG/DL	87	71		85	
T. BILI: 0.3-1.2 MG/DL	0.5	0.2		0.3	
D. BILI: 0.1-0.4 MG/DL	0.0	0.1		0.0	
CA: 9.0-11.0 MG/DL	9.7	9.7		9.9	
PO4: 3.0-4.5 MG/DL	2.5	1.9		2.7	
URIC A: 4.2-8.8 MG/DL	5.0	5.7		4.0	
T. PROT: 6.0-8.5 G/DL	6.9	6.9		6.9	
ALB.: 3.2-5.3 G/DL	4.3	4.4		4.4	
AST: 0-35 IU/L	19	17		25	
ALT: 0-30 IU/L	23	17		28	
ALK PHOS: 0-95 IU/L	66	77		69	
CHOL: 151-268 MG/DL	ND	ND		234	
LDH: 0-200 IU/L	ND	¹³⁵ ND		141	
CPK: 0-160 U/L (male)	ND	⁹³ ND	75	61	83

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{C}{M} \frac{F}{L}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>N.A.</u> ddmmmyy	<u>N.A.</u> ddmmmyy	<u>26 Oct 85</u> ddmmmyy	ddmmmyy	ddmmmyy	Date
NA: 135-148 MEQ/L			142			
K: 3.5-5.0 MEQ/L			4.2			
CL: 96-109 MEQ/L			104			
CO2: 24-30 MEQ/L			30			
SUN: 12-25 MG/DL			14			
CREAT: 0.4-1.5 MG/DL			0.8			
GLU: 70-115 MG/DL			93			
T. BILI: 0.3-1.2 MG/DL			0.3			
D. BILI: 0.1-0.4 MG/DL			0.1			
CA: 9.0-11.0 MG/DL			9.7			
PO4: 3.0-4.5 MG/DL			3.1			
URIC A: 4.2-8.8 MG/DL			4.3			
T. PROT: 6.0-8.5 G/DL			7.2			
ALB.: 3.2-5.3 G/DL			4.2			
AST: 0-35 IU/L			19			
ALT: 0-30 IU/L			30			
ALK PHOS: 0-95 IU/L			ND			
CHOL: 151-268 MG/DL			220			
LDH: 0-200 IU/L			ND			
CPK: 0-160 U/L (male)			63			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{C}{M} \frac{F}{L}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	<u>14 Oct 85</u> ddmmmyy	<u>21 Oct 85</u> ddmmmyy	<u>23 Oct 85</u> ddmmmyy	<u>26 Oct 85</u> ddmmmyy	_____ Date ddmmmyy
Hgb	13.9-16.3	15.8	15.5	16.0	15.7	
PCV	41.0-53.0	47.6	45.7	47.7	47.9	
Plt	150-350 K	189	196	198	219	
RBC	4.50-5.90	5.49	5.49	5.58	5.61	
WBC	4500-11000	6000	7600	6700	7600	
Bands	2-6%	2	4	3	7	
Polys	31-76%	45	52	57	53	
Eos	1-4%	2	1	2	2	
Bas		1	0	0	0	
Lymphs	24-44%	39	36	33	34	
Atyp Lym		0	0	0	1	
Monos	2-11%	11	6	5	3	
Other		0	0	0	0	
Retics	0.5-1.5%	N.D.	0.7	0.7	1.3	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{C}{M} \frac{F}{L}$	01	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

Clinical Pharmacology

TEST	NORMAL	Screen Predrug				Study	Date
		<u>N.D.</u> ddmmyy	<u>21 Oct 85</u> ddmmyy	<u>24 Oct 85</u> ddmmyy	<u>26 Oct 85</u> ddmmyy		
Color/Sp		N.D.	yellow clear	N.D.	N.D.		
Sp. Gr.		"	1.009	1.008	1.018		
pH		"	6.5	6.0	6.0		
Protein		"	neg	trace	neg		
Ketones		"	neg	neg	neg		
Occ Bld		"	neg	neg	neg		
Bili.		"	neg	neg	neg		
RBC		"	1	1	0		
WBC		"	0	1	0.2		
Casts		"	0	0	0		
Epi. Cel		"	1	0	0		
Crystals		"	0	0	0		
Bacteria		"	Few	0	0		

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
21 Oct 85	✓		
23 Oct 85	✓		
26 Oct 85	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>C</u> <u>F</u> <u>F</u> <u>M</u> <u>L</u>	<u>01</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#	dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
	(0-2400)	(0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
			<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug
#	dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
	(0-2400)	(0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
			<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K F L</u> <u>F M L</u>	<u>02</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
<u>1</u>	<u>23 OCT 85</u>	Screening laboratory
<u>1</u>	<u>25 OCT 85</u>	History, Physical Exam
<u>0</u>	<u>28 OCT 85</u>	Admission
<u>2</u>	<u>29 OCT 85</u>	<u>P.O.</u>
<u>5</u>	<u>01 NOV 85</u>	<u>I.V.</u>

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 02.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K E A</u> <u>F M L</u>	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 25 Oct 85
dd mm yy

Examiner

Brent G. Petty

Date of birth 02 Aug 60
In 870-20
dd mm yy

Brent G. Petty
print nameAge 25 yrsSex MRace B

	No	Yes	Comments
Allergy		✓	Penicillin → hives incl. an.
Tobacco Use	✓		
Alcohol Use		✓	3 cans
Recreational Drug Use		✓	3 joints/wk. tried cocaine months
Medications past 2 weeks	✓		
Experimental Drug Exposure	✓		
Blood or plasma donor	✓		
Prior Surgery		✓	adenoidectomy as a child
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	G.C. 10 years ago
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use			not asked
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
<u>Lietman</u>	<u>K E G</u> <u>F M L</u>	<u>02</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 25 OCT 85
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.0 C</u>	<u>76/min</u>	<u>22/min</u>	<u>124/78</u>	<u>182.5</u>	<u>64.4</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	<u>minimal tonsil palatins</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			<u>N.D.</u>
Rectal			<u>N.D.</u>
Extremities			
Skin		✓	<u>scars on hands from injury about 2 months ago</u>
Neurologic	✓		

CHEST X-RAY

Date 25 OCT 85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL	<input type="checkbox"/>	Describe abnormalities:

Examiner

Brent G. Petty
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{matrix} K & E & A \\ F & M & L \end{matrix}$	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01 Nov 85	0800	0830	IV	NA

Syringe + pyridox = 46.97817 g

Syringe = 21.87094 g

DOSAGE (total) 0.66 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>UG/mL</u>	RBC ACHe <u>uM/ml/min</u>
B01, B47	0	01 Nov 85	0750	0750	B01: *	B47: 14.48 14.48
B02	0.08	"	0805	0805	B02: *	
B03	0.16	"	0810	0810	B03: 4.38	
B04, B48	0.25	"	0815	0815	B04: 8.66	B48: 13.58
B05	0.33	"	0820	0820	B05: 6.66	
B06	0.42	"	0825	0825	B06: 8.52	
B07, B49	0.50	"	0830	0830	B07: 9.05	B49: 12.27
B08	0.58	"	0835	0835	B08: 1.14	
B09	0.66	"	0840	0840	B09: *	
B10, B50	0.75	"	0845	0845	B10: 4.73	B50: 12.56
B11	0.83	"	0850	0850	B11: 5.92	
B12	0.92	"	0855	0855	B12: 2.34	
B13, B51	1.0	"	0900	0900	B13: 1.42	B51: 13.34 13.34
B14, B52	1.33	"	0920	0920	B14: *	B52: 13.13
B15, B53	1.66	"	0940	0940	B15: *	B53: 13.67
B16, B54	2.0	"	1000	1000	B16: *	B54: 13.76
B17	2.5	"	1030	1030	B17: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	$\frac{K}{F} \frac{E}{M} \frac{J}{L}$	02	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01 Nov 85	0800	0830	IV	NA

DOSAGE (total) .66 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/mL	RBC AChE uM/ml/min
B18, B55	3.0	01 Nov 85	1100	1100	B18: *	B55: 14.80
B19	3.5	"	1130	1130	B19: *	
B20, B56	4.0	"	1200	1200	B20: *	B56: 15.00
B21	5.0	"	1300	1300	B21: *	
B22, B57	6.0	"	1400	1400	B22: *	B57: 14.75 14.80
B23	7.0	"	1500	1500	B23: *	
B24	8.0	"	1600	1600	B24: *	
B25	10.0	"	1800	1800	B25: *	
B26	12.0	"	2000	2000	B26: *	
B27, B58	24.0	02 Nov 85	0800	0800	B27: *	B58: 15.00

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	K E J F M L	02	Pyridostigmine
			PROTOCOL
			DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01 Nov 85	0800	0830	IV	NA

DOSAGE (total) .66 mg.

PHYSIOLOGIC VARIABLES

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	01 Nov 85	0750	0750	#84	#48/52	#OK
	0.8	"	0805	0805			
	0.16	"	0810	0810			
	0.25	"	0815	0815	#68		
	0.33	"	0820	0820			
	0.42	"	0825	0825			
	0.50	"	0830	0830	#64	#47/51	#ND
	0.58	"	0835	0835			
	0.66	"	0840	0840			
	0.75	"	0845	0845	#72		
	0.83	"	0850	0850			
	0.92	"	0855	0855			
	1.0	"	0900	0900	#68	#38/47	
	1.33	"	0920	0920	#68		
	1.66	"	0940	0940	#68		
	2.0	"	1000	1000	#72	#37/46	
	2.5	"	1030	1030			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K</u> <u>E</u> <u>G</u> <u>F</u> <u>M</u> <u>L</u>	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01 Nov 85	0800	0830	IV	NA

DOSAGE (total) 0.66 mg

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{K}{F} \frac{E}{M} \frac{D}{L}$	02	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	29 Oct 85	0805	0805	PO	NA

Syring + pyridox: 6.68746 g
 syring alone: 4.60945 g

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] $\mu\text{g/mL}$	RBC AChE $\mu\text{M/ml/min}$
B28, B59	0	29 Oct 85	0755	0755	B28: *	B59: 13.22
B29, B60	0.25	"	0820	0820	B29: *	B60: 14.46
B30, B61	0.50	"	0835	0835	B30: *	B61: 13.85
B31, B62	0.75	"	0850	0850	B31: *	B62: 14.38
B32, B63	1.0	"	0905	0905	B32: *	B63: 13.69
B33, B64	1.33	"	0925	0925	B33: 5.75	B64: 12.30
B34, B65	1.66	"	0945	0945	B34: 7.22	B65: 11.32
B35, B66	2.0	"	1005	1005	B35: 4.24	B66: 11.06
B36	2.5	"	1035	1035	B36: 5.50	
B37, B67	3.0	"	1105	1105	B37: 5.5	B67: 10.31
B38	3.5	"	1135	1135	B38: 3.92	
B39, B68	4.0	"	1205	1205	B39: 6.85	B68: 10.20
B40	5.0	"	1305	1305	B40: 2.76	
B41, B69	6.0	"	1405	1405	B41: 5.36	B69: 11.13
B42	7.0	"	1505	1505	B42: 2.34	
B43	8.0	"	1605	1605	B43: *	B69A: ND.
B44	10.0	"	1805	1805	B44: *	

* Belmar Small Animal Unit 157

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{K}{F} \frac{E}{M} \frac{D}{L}$	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
2	29 Oct 85	0805	0805	PO	NA

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K E G</u> <u>F M L</u>	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	290785	0805	0805	PO	NA

DOSAGE (total) 20mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	290785	0755	0755	# 84	# 41/45	# OK
	0.25	"	0820	0820	# 80		
	0.50	"	0835	0835	# 72	# 35/46	# OK
	0.75	"	0850	0850	# 64		
	1.0	"	0905	0905	# 68	# 39/50	
	1.33	"	0925	0925	# 64		
	1.66	"	0945	0945	# 60		
	2.00	"	1005	1005	# 60	# 37/50	
	2.5	"	1035	1035			
	3.0	"	1105	1105	# 60		
	3.5	"	1135	1135			
	4.0	"	1205	1205	# 74	# 31/40	
	5.0	"	1305	1305			
	6.0	"	1405	1405	# 82	# 42/49	
	7.0	"	1505	1505			
	8.0	"	1605	1605			
	10.0	"	1805	1805			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>F</u> <u>M</u> <u>L</u>	62	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	29 Oct 85	0805	0805	PO	NH

DOSAGE (total) 20mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{K}{F} \frac{E}{M} \frac{G}{L}$	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>23 Oct 85</u> ddmmmyy	<u>28 Oct 85</u> ddmmmyy	<u>29 Oct 85</u> ddmmmyy	<u>30 Oct 85</u> ddmmmyy	<u>01 Nov 85</u> ddmmmyy	Date
NA: 135-148 MEQ/L	ND	140		142 th		
K: 3.5-5.0 MEQ/L	ND	4.0		4.5		
CL: 96-109 MEQ/L	ND	106		108		
CO2: 24-30 MEQ/L	ND	27		28		
SUN: 12-25 MG/DL	13	16		14		
CREAT: 0.4-1.5 MG/DL	11	1.1		1.1		
GLU: 70-115 MG/DL	72	71		83		
T. BILI: 0.3-1.2 MG/DL	0.4	1.2		0.7		
D. BILI: 0.1-0.4 MG/DL	0.0	0.0		0.0		
CA: 9.0-11.0 MG/DL	10.2	9.8		9.8		
PO4: 3.0-4.5 MG/DL	3.6	3.7		4.0		
URIC A: 4.2-8.8 MG/DL	5.6	5.7		5.1		
T. PROT: 6.0-8.5 G/DL	7.6	7.3		6.9		
ALB.: 3.2-5.3 G/DL	5.0	4.8		4.6		
AST: 0-35 IU/L	28	23		21		
ALT: 0-30 IU/L	26	19		14		
ALK PHOS: 0-95 IU/L	61	62		55		
CHOL: 151-268 MG/DL	199	175		174		
LDH: 0-200 IU/L	ND	134		118		
CPK: 0-160 U/L (male)	ND	228	140	120	116	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>KEG</u> F M L	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NA</u> ddmmmyy	<u>NA</u> ddmmmyy	<u>02NN85</u> ddmmmyy	ddmmmyy	ddmmmyy	Date
NA: 135-148 MEQ/L			145			
K: 3.5-5.0 MEQ/L			4.1			
CL: 96-109 MEQ/L			101			
CO2: 24-30 MEQ/L			24			
SUN: 12-25 MG/DL			19			
CREAT: 0.4-1.5 MG/DL			1.2			
GLU: 70-115 MG/DL			78			
T. BILI: 0.3-1.2 MG/DL			1.2			
D. BILI: 0.1-0.4 MG/DL			0.0			
CA: 9.0-11.0 MG/DL			N.D			
PO4: 3.0-4.5 MG/DL			3.5			
URIC A: 4.2-8.8 MG/DL			5.6			
T. PROT: 6.0-8.5 G/DL			8.1			
ALB.: 3.2-5.3 G/DL			5.0			
AST: 0-35 IU/L			22			
ALT: 0-30 IU/L			18			
ALK PHOS: 0-95 IU/L			57			
CHOL: 151-268 MG/DL			205			
LDH: 0-200 IU/L			131			
CPK: 0-160 U/L (male)			128			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	TK E 9 M L	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen	Predrug	Study			
TEST	NORMAL	<u>23 Oct 85</u> ddmmmyy	<u>28 Oct 85</u> ddmmmyy	<u>30 Oct 85</u> ddmmmyy	<u>02 Nov 85</u> ddmmmyy	_____ ddmmmyy	Date
Hgb	13.9-16.3	13.9	13.6	14.1	15.0		
PCV	41.0-53.0	41.0	41.2	41.7	44.6		
Plt	150-350	362	391	375	410		
RBC	4.50-5.90	4.63	4.81	4.82	5.22		
WBC	4500-11000	6100	6200	6600	5700		
Bands	2-6%	1	1	8	11		
Polys	31-76%	42	47	30	38		
Eos	1-4%	7	8	10	3		
Bas		0	0	1	1		
Lymphs	24-44%	44	38	41	37		
Atyp Lym		0	0	1	0		
Monos	2-11%	6	6	9	0		
Other		0	0	0	0		
Retics	0.5-1.5%	ND	0.9	0.9	1.0		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K E G</u> <u>F M L</u>	02	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University of Maryland
Johns Hopkins Hospital
Clinical Pharmacology*

TEST	NORMAL	Screen	Predrug	Study		Date
		25 Oct 85 ddmmmyy	28 Oct 85 ddmmmyy	30 Oct 85 ddmmmyy	02 Nov 85 ddmmmyy	
Color/Sp		ND	ND	ND	ND	
Gr.		1.023	1.027	1.023	ND	
pH		6.5	6.0	6.0	6.0	
Protein		Trace	Trace	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	1	0	rare	
WBC		0	1	0	rare	
Casts		0	0	0	0	
Epi. Cel		0	0	1	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
25 Oct 85		✓	non-specific ST-T changes
28 Oct 85		✓	non-specific ST-T changes, min. change between tracings
30 Oct 85		✓	non-specific ST-T changes, min change between tracings
02 Nov 85		✓	non-specific ST-T changes, min change between tracings

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>K</u> <u>E</u> <u>9</u> <u>F</u> <u>M</u> <u>L</u>	<u>02</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		__ __ __ dd mmm yy	__ __ __ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		<input type="checkbox"/> (0-2400)	<input type="checkbox"/> (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> UNKNOWN	
#		__ __ __ dd mmm yy	__ __ __ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		<input type="checkbox"/> (0-2400)	<input type="checkbox"/> (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A I G</u> F M L	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	24 OCT 85	Screening laboratory
—	25 OCT 85	History, Physical Exam
0	28 OCT 85	Admission
2	29 OCT 85	I.V.
5	01 NOV 85	OPAL

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 03.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt G. Pitty M. D.
Investigator's signature

24, Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A I G</u> <u>F M L</u>	<u>03</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 25/OCT/85
dd mmm yyExaminer Brent G. PettyDate of birth 26/JUN/58
dd mmm yyBrent G. Petty
print nameAge 27 yrsSex MRace B

	No	Yes	Comments
Allergy		✓	hay fever, dust congestion 2 AM resolves spontaneously in 10-15 min
Tobacco Use		✓	2 1/2 PPD
Alcohol Use		✓	rarely
Recreational Drug Use		✓	marijuana tried 7-14 yrs ago
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	"Pharma-Kinetics" 2-3 months ago was last; 2 before that
Blood or plasma donor		✓	Last 4-5 yrs. ago
Prior Surgery		✓	Ⓡ achilles tendon repair 10/84 skin grafts to both hands after burn age 12
Eye, ear, nose, throat		✓	hay fever / congestion as above
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC ~ 10 yrs ago - Rx PCN
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use			Not asked
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A I G</u> F M L	<u>03</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATIONDate 10/Oct/8525
Add mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.2 C</u>	<u>90/min</u>	<u>20/min</u>	<u>130/70</u>	<u>175.2</u>	<u>89.9</u>

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		
Chest, lungs			<u>Not done</u>
Heart	✓		
Abdomen	✓		
Genitalia			<u>Not done</u>
Rectal			<u>Not done</u>
Extremities	✓		
Skin	✓		<u>Scar (D) lower leg, on hands</u>
Neurologic	✓		

CHEST X-RAYDate 25/OCT/85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MDBrent G. Petty

print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{T}{M} \frac{G}{L}$	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	29 Oct 85	0800	0830	IV	NA

syringe + pyridox = 41.98
syringe alone = 21.93

DOSAGE (total) .66 mg.**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>UG/mL</u>	RBC AChE <u>uM/ml/min</u>
B01, B47	0	29 Oct 85	0755	0755	B01: *	B47: 12.59
B02	0.08	"	0805	0805	B02: 5.59	
B03	0.16	"	0810	0810	B03: 5.90	
B04, B48	0.25	"	0815	0815	B04: 8.81	B48: 12.06
B05	0.33	"	0820	0820	B05: 7.89	
B06	0.42	"	0825	0825	B06: 9.85	
B07, B49	0.50	"	0830	0830	B07: 10.7	B49: 11.28
B08	0.58	"	0835	0835	B08: 5.96	
B09	0.66	"	0840	0840	B09: 4.21	
B10, B50	0.75	"	0845	0845	B10: 2.74	B50: 10.49
B11	0.83	"	0850	0850	B11: 2.52	
B12	0.92	"	0855	0855	B12: 2.49	
B13, B51	1.0	"	0900	0900	B13: *	B51: 11.74
B14, B52	1.33	"	0920	0920	B14: *	B52: 11.66
B15, B53	1.66	"	0940	0940	B15: *	B53: 12.22
B16, B54	2.0	"	1000	1000	B16: *	B54: 12.60
B17	2.5	"	1030	1030	B17: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	<u>A</u> <u>I</u> <u>G</u> <u>F</u> <u>M</u> <u>L</u>	03	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	290585	0800	0830	IV	NA

DOSAGE (total) .66 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>uM/mL</u>	RBC AChE <u>uM/mL/min</u>
B18, B55	3.0	290585	1100	1100	B18: *	B55: 12.71
B19	3.5	"	1130	1130	B19: *	
B20, B56	4.0	"	1200	1200	B20: *	B56: 12.26
B21	5.0	"	1300	1300	B21: *	
B22, B57	6.0	"	1400	1400	B22: *	B57: 12.38
B23	7.0	"	1500	1506	B23: *	
B24	8.0	"	1600	1600	B24: *	
B25	10.0	"	1800	1800	B25: *	
B26	12.0	"	2000	2000	B26: *	
B27, B58	24.0	300585	0800	0804	B27: *	B58: 13.34

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{T}{M} \frac{G}{L}$	03	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	290885	0800	0830	IV	NA

DOSAGE (total) .66 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	290885	0755	0755	#70	#30/33	#ok
	0.8	"	0805	0805			
	0.16	"	0810	0810			
	0.25	"	0815	0815	#68		
	0.33	"	0820	0820			
	0.42	"	0825	0825			
	0.50	"	0830	0830	#64	#37/42	#ok
	0.58	"	0835	0835			
	0.66	"	0840	0840			
	0.75	"	0845	0845	#68		
	0.83	"	0850	0850			
	0.92	"	0855	0855			
	1.0	"	0900	0900	#68	#33/46	
	1.33	"	0920	0920	#66		
	1.66	"	0940	0940	#62		
	2.0	"	1000	1000	#70	#30/41	
	2.5	"	1030	1030			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{T}{M} \frac{G}{L}$	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01N85	0805	0805	PO	NA.

syringe + syringe = 6.73982 DOSAGE (total) 20 mg.
syringe alone = 4.66188

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] $\mu\text{g/mL}$	RBC AChE $\mu\text{M/mL/min}$
B28, B59	0	01N85	0745	0745	B28: *	B59: 13.37 ^{13.28} ss
B29, B60	0.25	"	0820	0820	B29: *	B60: 13.26
B30, B61	0.50	"	0835	0835	B30: *	B61: 13.08
B31, B62	0.75	"	0850	0850	B31: 6.80	B62: 12.90
B32, B63	1.0	"	0905	0905	B32: 6.07	B63: 11.81
B33, B64	1.33	"	0925	0925	B33: 7.25	B64: 11.06
B34, B65	1.66	"	0945	0945	B34: 7.49	B65: 10.06 ^{10.60} ss
B35, B66	2.0	"	1005	1005	B35: 9.82	B66: 10.09
B36	2.5	"	1035	1035	B36: 10.7	
B37, B67	3.0	"	1105	1105	B37: 12.0	B67: 9.64
B38	3.5	"	1135	1135	B38: 10.7	
B39, B68	4.0	"	1205	1205	B39: 10.5	B68: 10.10
B40	5.0	"	1305	1305	B40: *	
B41, B69	6.0	"	1405	1405	B41: 3.36	B69: 11.12
B42	7.0	"	1505	1505	B42: 2.13	
B43	8.0	"	1605	1608	B43: 2.55	B69A: N.D.
B44	10.0	"	1805	1805	B44: *	

* Below assay sensitivity 173

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	<u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{T}{M} \frac{G}{L}$	03	PROTOCOL	<u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01N285	0805	0805	PO	NA

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 174

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>T</u> <u>G</u> F M L	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	01 Nov 85	0805	0805	PO	NA

DOSAGE (total) 20 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	01 Nov 85	0745	0745	#64	#40/37	#ok
	0.25	"	0820	0820	#78		
	0.50	"	0835	0835	#64	#37/45	#ok
	0.75	"	0850	0850	#68		
	1.0	"	0905	0905	#70	#36/53	
	1.33	"	0925	0925	#64		
	1.66	"	0945	0945	#64		
	2.00	"	1005	1005	#60	#40/44	
	2.5	"	1035	1035			
	3.0	"	1105	1105	#60		
	3.5	"	1135	1135			
	4.0	"	1205	1205	#56	#42/40	
	5.0	"	1305	1305			
	6.0	"	1405	1405	#70	#44/44	
	7.0	"	1505	1505			
	8.0	"	1605	1608			
	10.0	"	1805	1805			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A I G</u> <u>F M L</u>	<u>03</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>24 Oct 85</u> ddmmmyy	<u>28 Oct 85</u> ddmmmyy	<u>29 Oct 85</u> ddmmmyy	<u>30 Oct 85</u> ddmmmyy	<u>01 Nov 85</u> ddmmmyy	Date
NA: 135-148 MEQ/L	141	139		137		
K: 3.5-5.0 MEQ/L	4.5	4.3		4.3		
CL: 96-109 MEQ/L	105	100		103		
CO2: 24-30 MEQ/L	24	27		26		
SUN: 12-25 MG/DL	9	12		14		
CREAT: 0.4-1.5 MG/DL	0.9	0.8		0.9		
GLU: 70-115 MG/DL	88	86		83		
T. BILI: 0.3-1.2 MG/DL	0.4	0.4		0.4		
D. BILI: 0.1-0.4 MG/DL	0.0	0.0		0.0		
CA: 9.0-11.0 MG/DL	9.7	9.8		9.7		
PO4: 3.0-4.5 MG/DL	3.9	3.8		4.3		
URIC A: 4.2-8.8 MG/DL	3.6	3.3		3.8		
T. PROT: 6.0-8.5 G/DL	7.1	7.2		6.8		
ALB.: 3.2-5.3 G/DL	4.5	4.4		4.5		
AST: 0-35 IU/L	22	16		15		
ALT: 0-30 IU/L	15	20		17		
ALK PHOS: 0-95 IU/L	80	84		79		
CHOL: 151-268 MG/DL	ND	193		220		
LDH: 0-200 IU/L	ND	93		83		
CPK: 0-160 U/L (male)	ND	193	145	125	119	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A T G</u> <u>F M L</u>	<u>03</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

TEST: NORMAL	Screen Predrug		Study	
	<u>NA</u> ddmmmyy	<u>NA</u> ddmmmyy	<u>02 Nov 85</u> ddmmmyy	Date
NA: 135-148 MEQ/L			137	
K: 3.5-5.0 MEQ/L			4.0	
CL: 96-109 MEQ/L			98	
CO2: 24-30 MEQ/L			26	
SUN: 12-25 MG/DL			12	
CREAT: 0.4-1.5 MG/DL			0.9	
GLU: 70-115 MG/DL			84	
T. BILI: 0.3-1.2 MG/DL			0.6	
D. BILI: 0.1-0.4 MG/DL			0.1	
CA: 9.0-11.0 MG/DL			ND	
PO4: 3.0-4.5 MG/DL			4.7	
URIC A: 4.2-8.8 MG/DL			3.7	
T. PROT: 6.0-8.5 G/DL			7.6	
ALB.: 3.2-5.3 G/DL			4.9	
AST: 0-35 IU/L			17	
ALT: 0-30 IU/L			22	
ALK PHOS: 0-95 IU/L			74	
CHOL: 151-268 MG/DL			220	
LDH: 0-200 IU/L			84	
CPK: 0-160 U/L (male)			137	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A T G</u> <u>F M L</u>	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

TEST	NORMAL	Screen	Predrug	Study		
		24 Oct 85 ddmmmyy	28 Oct 85 ddmmmyy	30 Oct 85 ddmmmyy	02 Nov 85 ddmmmyy	_____ Date ddmmmyy
Hgb	13.9-16.3	13.4	13.4	13.6	13.3	
PCV	41.0-53.0	41.0	40.9	45.0	41.1	
Plt	150-350	286	263	289	271	
RBC	4.50-5.90	4.96	4.86	5.57	4.89	
WBC	4500-11000	5300	6800	6400	6900	
Bands	2-6%	5	3	10	0	
Polys	31-76%	56	53	47	66	
Eos	1-4%	4	8	8	0	
Bas		1	1	1	0	
Lymphs	24-44%	29	27	22	26	
Atyp Lym		0	2	0	0	
Monos	2-11%	5	6	12	8	
Other		0	0	0	0	
Retics	0.5-1.5%	N.D.	1.6	1.7	2.0	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A T G</u> <u>F M L</u>	03	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University of Maryland
Johns Hopkins Hospital
Clinical Pharmacology*

Screen Predrug

Study

TEST	NORMAL	25 Oct 85 ddmmmyy	28 Oct 85 ddmmmyy	30 Oct 85 ddmmmyy	02 Nov 85 ddmmmyy	_____ Date ddmmmyy
Color/Sp		ND	ND	ND	ND	
Sp. Gr.		1.021	1.014	1.018	ND	
pH		6.5	6.0	6.5	6.0	
Protein		Trace	neg	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		1	0	0	none	
WBC		0	0	2	0-1	
Casts		0	0	0	0	
Epi. Cel		0	0	0	occasional	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
25 Oct 85	✓		
28 Oct 85	✓		
30 Oct 85	✓		
02 Nov 85	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A I G</u> <u>F M L</u>	<u>03</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	<u>04</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	18 Nov 85	Screening laboratory
—	19 Nov 85	History, Physical Exam
0	21 Nov 85	Admission
2	22 Nov 85	P.O.
5	25 Nov 85	I.V.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 04.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt J. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	<u>04</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 19 Nov 85
dd mmm yy

Examiner Brent G Petty

Date of birth 14 Sep 60
dd mmm yy

Brent Petty
print name

Age 25 yrs

Sex m

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	<u>10 PD</u>
Alcohol Use		✓	<u>6 pack / weekend</u>
Recreational Drug Use		✓	<u>mg q 2 weeks</u>
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	<u>Tobramycin, Interferon</u>
Blood or plasma donor		✓	<u>last 1984</u>
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal		✓	<u>fx hip as child</u>
Neuropsychiatric	✓		
Pesticide/herbicide use	✓	✓	
Other <u>Pets</u>		✓	<u>Birds, dogs 3 recent Rx for Fleas</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	<u>04</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 19/Nov/85
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.8</u> C	<u>68</u> /min	<u>20</u> /min	<u>106/58</u>	<u>174.0</u>	<u>63.5</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	poor dental hygiene some gingivitis mild arterioles narrowing
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			ND
Rectal			ND
Extremities		✓	scar (L) forearm mild antecubital scarring from studies + blood donation
Skin	✓		
Neurologic	✓		

CHEST X-RAY

Date 19/Nov/85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL	<input type="checkbox"/>	Describe abnormalities:

Examiner

Brent G. Petty
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0850	0920	IV	NA

Syringe + Pyrid. = 41.38393 g
 syringe alone = 21.39470 g

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	25 Nov 85	0845	0845	B01: *	B47: 13.20
B02	0.08	"	0855	0855	B02: 15.4	
B03	0.16	"	0900	0900	B03: 24.5	
B04, B48	0.25	"	0905	0905	B04: 27.1	B48: 10.54
B05	0.33	"	0910	0910	B05: 30.5	
B06	0.42	"	0915	0915	B06: 37.6	
B07, B49	0.50	"	0920	0920	B07: 37.5	B49: 8.50
B08	0.58	"	0925	0925	B08: 18.6	
B09	0.66	"	0930	0930	B09: 13.4	
B10, B50	0.75	"	0935	0935	B10: 12.0	B50: 9.70
B11	0.83	"	0940	0940	B11: 10.3	
B12	0.92	"	0945	0945	B12: 8.50	
B13, B51	1.0	"	0950	0950	B13: 8.34	B51: 10.12
B14, B52	1.33	"	1010	1010	B14: 5.87	B52: 11.01
B15, B53	1.66	"	1030	1030	B15: 3.80	B53: 10.02
B16, B54	2.0	"	1050	1050	B16: 3.40	B54: 10.77
B17	2.5	"	1120	1120	B17: 3.08	

* below assay sensitivity 185

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	$\frac{A}{F} \frac{R}{M} \frac{K}{L}$	04	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0850	0920	IV	NA

DOSAGE (total)

1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	25 Nov 85	1150	1150	B18: 1.51	B55: 11.99
B19	3.5	"	1220	1220	B19: *	
B20, B56	4.0	"	1250	1250	B20: *	B56: 12.41
B21	5.0	"	1350	1350	B21: N.S.	
B22, B57	6.0	"	1450	1450	B22: 1.67	B57: 12.55
B23	7.0	"	1550	1550	B23: *	
B24	8.0	"	1650	1650	B24: *	
B25	10.0	"	1850	1850	B25: *	
B26	12.0	"	2050	2050	B26: *	
B27, B58	24.0	26 Nov 85	0850	0850	B27: *	B58: 12.59

* below assay sensitivity N.S. = no sample

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{R}{M} \frac{K}{L}$	04	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0850	0920	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	25 Nov 85	0845	0845	#70	#33/39	#OK
	0.8	"	0855	0855			
	0.16	"	0900	0900			
	0.25	"	0905	0905	#74		
	0.33	"	0910	0910			
	0.42	"	0915	0915			
	0.50	"	0920	0920	#68	#38/40	#OK
	0.58	"	0925	0925			
	0.66	"	0930	0930			
	0.75	"	0935	0935	#68		
	0.83	"	0940	0940			
	0.92	"	0945	0945			
	1.0	"	0950	0950	#70	#35/32	
	1.33	"	1010	1010	#66		
	1.66	"	1030	1030	#72		
	2.0	"	1050	1050	#74	#36/32	
	2.5	"	1120	1120			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>R</u> <u>K</u> <u>F</u> <u>M</u> <u>L</u>	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0850	0920	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{Q}{M} \frac{K}{L}$	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0845	0845	PO	N/A

pyridostigmine + pyridostigmine = 6.72348
pyridostigmine alone = 4.64543

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	22 Nov 85	0845	0845	B28: *	B59: 13.87
B29, B60	0.25	"	0900	0900	B29: *	B60: 13.39
B30, B61	0.50	"	0915	0915	B30: *	B61: 13.98
B31, B62	0.75	"	0930	0930	B31: 2.23	B62: 13.23
B32, B63	1.0	"	0945	0945	B32: 7.93	B63: 11.79
B33, B64	1.33	"	1005	1005	B33: 8.53	B64: 10.98
B34, B65	1.66	"	1025	1025	B34: 11.2	B65: 9.77
B35, B66	2.0	"	1045	1045	B35: 16.5	B66: 9.02
B36	2.5	"	1115	1115	B36: 17.1	
B37, B67	3.0	"	1145	1145	B37: 18.8	B67: 8.30
B38	3.5	"	1215	1215	B38: 18.0	
B39, B68	4.0	"	1245	1245	B39: 20.3	B68: 7.57
B40	5.0	"	1345	1445*	B40: 14.7	
B41, B69	6.0	"	1445	1445	B41: 10.10	B69: 9.63
B42	7.0	"	1545	1545	B42: 7.90	
B43	8.0	"	1645	1645	B43: 7.25	B69A: 11.23
B44	10.0	"	1845	1840	B44: 3.10	

*below assay sensitivity

* Copied from original worksheet

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{A}{F} \frac{R}{M} \frac{K}{L}$	04	Pyridostigmine
			PROTOCOL
			DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
3	22 Nov 85	0845	0845	PO	N/A

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>R</u> <u>K</u> F M L	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0845	0845	PO	NA

DOSAGE (total) 20 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
1	0	22 Nov 85	0845	0845	# 80	# 35/38	# ok
	0.25	"	0900	0900	# 74		
	0.50	"	0915	0915	# 74	# 26/36	# ok
	0.75	"	0930	0930	# 76		
	1.0	"	0945	0945	# 70	# 25/29	
	1.33	"	1005	1005	# 72		
	1.66	"	1025	1025	# 62		
	2.00	"	1045	1045	# 60	# 26/34	
	2.5	"	1115	1115			
	3.0	"	1145	1145	# 70		
	3.5	"	1215	1215			
	4.0	"	1245	1245	# 74	# 27/29	
	5.0	"	1345	1345			
	6.0	"	1445	1445	# 76	# 25/26	
	7.0	"	1545	1545 1645 20			
	8.0	"	1645	1645			
	10.0	"	1845	1845			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	18 Nov 85 ddmmmyy	21 Nov 85 ddmmmyy	23 Nov 85 ddmmmyy	26 Nov 85 ddmmmyy	Date ddmmmyy
NA: 135-148 MEQ/L	142	ND	139	137	
K: 3.5-5.0 MEQ/L	4.0	ND	4.3	4.6	
CL: 96-109 MEQ/L	104	ND	102	102	
CO2: 24-30 MEQ/L	22	ND	24	26	
SUN: 12-25 MG/DL	11	21	16	20	
CREAT: 0.4-1.5 MG/DL	1.0	1.0	1.0	1.0	
GLU: 70-115 MG/DL	68	141	111	117	
T. BILI: 0.3-1.2 MG/DL	1.1	1.5	1.3	1.4	
D. BILI: 0.1-0.4 MG/DL	0.2	0.1	0.1	0.1	
CA: 9.0-11.0 MG/DL	9.9	9.8	9.8	9.7	
PO4: 3.0-4.5 MG/DL	3.8	4.1	4.3	4.5	
URIC A: 4.2-8.8 MG/DL	5.5	5.1	6.2	6.0	
T. PROT: 6.0-8.5 G/DL	7.5	7.1	7.6	7.2	
ALB.: 3.2-5.3 G/DL	4.9	4.7	4.9	5.0	
AST: 0-35 IU/L	23	22	13	17	
ALT: 0-30 IU/L	10	8	10	11	
ALK PHOS: 0-95 IU/L	71	67	60	57 57 5.7	
CHOL: 151-268 MG/DL	ND	ND	ND	ND	
LDH: 0-200 IU/L	ND	117	119	117	
CPK: 0-160 U/L (male)	ND	102	80	83	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{R}{M} \frac{K}{L}$	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUESLaboratory Johns Hopkins Hospital

		Screen	Predrug	Study		
		18 Nov 85	21 Nov 85	23 Nov 85	26 Nov 85	Date
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy
Hgb	13.9-16.3	14.7	14.6	15.3	14.4	
PCV	41.0-53.0	43.6	43.6	45.8	42.9	
Plt	150-350	267	263	273	271	
RBC	4.50-5.90	4.64	4.61	4.79	4.48	
WBC	4500-11000	5000	6900	4900	5000	
Bands	2-6%	0	9	10	10	
Polys	31-76%	76	67	44	45	
Eos	1-4%	1	0	4	2	
Bas		0	0	0	0	
Lymphs	24-44%	17	16	31	31	
Atyp Lym		0	0	2	1	
Monos	2-11%	6	8	9	11	
Other		0	0	0	0	
Retics	0.5-1.5%	<u>1.7</u>	1.1	1.3	1.2	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A R K</u> <u>F M L</u>	04	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University
Johns Hopkins Hospital in
Clinical Pharmacology*

TEST	NORMAL	Screen		Predrug		Study	
		18 Nov 85 ddmmmyy	21 Nov 85 ddmmmyy	25 Nov 85 ddmmmyy	26 Nov 85 ddmmmyy	----- ddmmmyy	Date
Color/Sp		ND	ND	ND	ND		
Gr.		1.001	1.015	1.011	1.016		
pH		6.0	7.0	5.0	5.0		
Protein		Neg	Trace	Trace	Trace		
Ketones		Neg	Neg	Neg	Neg		
Occ Bld		Neg	Neg	Neg	Neg		
Bili.		Neg	Neg	Neg	Neg		
RBC		0	0	0	0		
WBC		0	0	0	0		
Casts		0	0	0	0		
Epi. Cel		0	0	0	0		
Crystals		0	0	0	0		
Bacteria		0	0	0	0		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
19 Nov 85	✓		
23 Nov 85	✓		
26 Nov 85	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>R</u> <u>K</u> F M L	<u>04</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		____	____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		dd mmm yy	dd mmm yy	Mild	DEF.	None
		____	____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		(0-2400)	(0-2400)	Mod	PROB.	Treatment
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
				Sev	POSS.	Stop test drug
					DEF. NOT	
					UNKNOWN	
#		____	____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		dd mmm yy	dd mmm yy	Mild	DEF.	None
		____	____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		(0-2400)	(0-2400)	Mod	PROB.	Treatment
				<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
				Sev	POSS.	Stop test drug
					DEF. NOT	
					UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E</u> <u>m</u> <u>K</u> <u>F</u> <u>M</u> <u>L</u>	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmmyy	Procedures
—	19 Nov 85	Screening laboratory
—	20 Nov 85	History, Physical Exam
0	21 Nov 85	Admission
2	22 Nov 85	P.O.
5	25 Nov 85	I.V.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 05.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Robert G. Pitter M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E m k</u> <u>F M L</u>	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 20/Nov/85
dd mmm yy

Examiner Brent G. Petty MD

Date of birth 21/APR/63
dd mmm yy

Brent G. Petty
print name

Age 22 yrs

Sex M

Race B

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1 pk. / month
Alcohol Use		✓	6 pk. / month
Recreational Drug Use		✓	MD, last exposure last year
Medications past 2 weeks		✓	Tylenol 1 week ago for flu
Experimental Drug Exposure	✓		
Blood or plasma donor	✓		
Prior Surgery		✓	I+D over (R) 3rd MCP joint 1982
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		
Other <u>Pets</u>			<u>dogs 5 Flea Powder</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E M K</u> <u>F M L</u>	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 20 Nov 85
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4</u> C	<u>90</u> min	<u>20</u> min	<u>110/76</u>	<u>167.0</u>	<u>60.3</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	SI ↑ @ tonsils erythema or exudate tonsils gelatinous
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			N.D.
Rectal			N.D.
Extremities	✓		
Skin		✓	Scar @ shoulder, scar @ 3rd m.c.f., on abdomen
Neurologic	✓		

CHEST X-RAY

Date 20 Nov 85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{F}{F} \frac{M}{M} \frac{K}{L}$	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0855	0925	IV	NA

Syringe + pyrido: 41.50949g DOSAGE (total) 1.32 mg.
 syringe alone: 21.51132

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>NG/mL</u>	RBC AChE <u>uM/ml/min</u>
B01, B47	0	25 Nov 85	0850	0850	B01: *	B47: 13.35
B02	0.08	"	0900	0900	B02: 17.3	
B03	0.16	"	0905	0905	B03: 37.1	
B04, B48	0.25	"	0910	0910	B04: 38.7	B48: 11.04
B05	0.33	"	0915	0915	B05: 38.8	
B06	0.42	"	0920	0920	B06: 31.9	
B07, B49	0.50	"	0925	0925	B07: 31.3	B49: 8.89
B08	0.58	"	0930	0930	B08: 30.2	
B09	0.66	"	0935	0935	B09: 22.0	
B10, B50	0.75	"	0940	0940	B10: 16.2	B50: 9.78
B11	0.83	"	0945	0945	B11: 16.8	
B12	0.92	"	0950	0950	B12: 11.7	
B13, B51	1.0	"	0955	0955	B13: 11.7	B51: 10.38
B14, B52	1.33	"	1015	1015	B14: 5.74	B52: 10.87
B15, B53	1.66	"	1035	1035	B15: 5.93	B53: 10.59
B16, B54	2.0	"	1055	1055	B16: 4.37	B54: 11.10
B17	2.5	"	1125	1125	B17: 2.52	

* below assay sensitivity 200

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	$\begin{matrix} E & M & K \\ F & M & L \end{matrix}$	05	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0855	0925	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE $\mu\text{M/ml/min}$
B18, B55	3.0	25 Nov 85	1155	1155	B18: 4.56	B55: 12.41
B19	3.5	"	1225	1225	B19: 3.65	
B20, B56	4.0	"	1255	1255	B20: *	B56: 12.72
B21	5.0	"	1355	1355	B21: *	
B22, B57	6.0	"	1455	1455	B22: *	B57: 13.24
B23	7.0	"	1555	1555	B23: *	
B24	8.0	"	1655	1655	B24: *	
B25	10.0	"	1855	1855	B25: 2.14	
B26	12.0	"	2055	2055	B26: *	
B27, B58	24.0	26 Nov 85	0855	0855	B27: *	B58: 12.91

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E M JS</u> <u>F M L</u>	<u>05</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>25 Nov 85</u>	<u>0855</u>	<u>0955</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	<u>0</u>	<u>25 Nov 85</u>	<u>0850</u>	<u>0850</u>	<u>#78</u>	<u>#23/29</u>	<u>#OK</u>
	<u>0.8</u>	<u>"</u>	<u>0900</u>	<u>0900</u>			
	<u>0.16</u>	<u>"</u>	<u>0905</u>	<u>0905</u>			
	<u>0.25</u>	<u>"</u>	<u>0910</u>	<u>0910</u>	<u>#64</u>		
	<u>0.33</u>	<u>"</u>	<u>0915</u>	<u>0915</u>			
	<u>0.42</u>	<u>"</u>	<u>0920</u>	<u>0920</u>			
	<u>0.50</u>	<u>"</u>	<u>0925</u>	<u>0925</u>	<u>#64</u>	<u>#47/49</u>	<u>#OK</u>
	<u>0.58</u>	<u>"</u>	<u>0930</u>	<u>0930</u>			
	<u>0.66</u>	<u>"</u>	<u>0935</u>	<u>0935</u>			
	<u>0.75</u>	<u>"</u>	<u>0940</u>	<u>0940</u>	<u>#60</u>		
	<u>0.83</u>	<u>"</u>	<u>0945</u>	<u>0945</u>			
	<u>0.92</u>	<u>"</u>	<u>0950</u>	<u>0950</u>			
	<u>1.0</u>	<u>"</u>	<u>0955</u>	<u>0955</u>	<u>#68</u>	<u>#36/37</u>	
	<u>1.33</u>	<u>"</u>	<u>1015</u>	<u>1015</u>	<u>#68</u>		
	<u>1.66</u>	<u>"</u>	<u>1035</u>	<u>1035</u>	<u>#70</u>		
	<u>2.0</u>	<u>"</u>	<u>1055</u>	<u>1055</u>	<u>#64</u>	<u>#38/42</u>	
	<u>2.5</u>	<u>"</u>	<u>1125</u>	<u>1125</u>			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{F}{F} \frac{M}{M} \frac{K}{L}$	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25NN85	0855	0925	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E M K</u> <u>F M L</u>	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0850	0850	PO	NA

siging + pyridos = 6.71525
siging alone = 4.61032

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	22 Nov 85	0800	0800	B28: *	B59: 13.86
B29, B60	0.25	"	0905	0910	B29: *	B60: 13.53
B30, B61	0.50	"	0920	0925	B30: 8.24	B61: 12.73
B31, B62	0.75	"	0935	0935	B31: 14.0	B62: 11.83
B32, B63	1.0	"	0950	0950	B32: 19.9	B63: 10.13
B33, B64	1.33	"	1010	1010	B33: 22.0	B64: 9.17
B34, B65	1.66	"	1030	1030	B34: 20.0	B65: 8.87
B35, B66	2.0	"	1050	1050	B35: 25.7	B66: 8.42
B36	2.5	"	1120	1120	B36: 17.1	
B37, B67	3.0	"	1150	1150	B37: 15.0	B67: 9.34
B38	3.5	"	1220	1220	B38: 13.4	
B39, B68	4.0	"	1250	1250	B39: 9.42	B68: 9.79
B40	5.0	"	1350	1350	B40: 4.98	
B41, B69	6.0	"	1450	1450	B41: 3.73	B69: 12.12
B42	7.0	"	1550	1550	B42: 3.62	
B43	8.0	"	1650	1650	B43: 3.57	B69A: 12.93
B44	10.0	"	1850	1850	B44: 1.41	

* below assay sensitivity 204

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0850	0850	PO	NA

DOSAGE (total) 20mg.

PLASMA CONCENTRATIONS

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E M K</u> <u>F M L</u>	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0850	0850	PO	NA

DOSAGE (total) 20 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	22 Nov 85	0800	0800	# 78	# 40/45	#
	0.25	"	0905	0905	# 78		
	0.50	"	0920	0920	# 80	# 35/44	#
	0.75	"	0935	0935	# 82		
	1.0	"	0950	0950	# 76	# 38/48	
	1.33	"	1010	1010	# 72		
	1.66	"	1030	1030	# 72		
	2.00	"	1050	1050	# 74	# 41/48	
	2.5	"	1120	1120			
	3.0	"	1150	1150	# 70		
	3.5	"	1220	1220			
	4.0	"	1250	1250	# 78	# 49/55 55/49	
	5.0	"	1350	1350		2R	
	6.0	"	1450	1450	# 70	# 45/48 48/45	
	7.0	"	1550	1550		2R	
	8.0	"	1650	1650			
	10.0	"	1850	1850			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>F M K</u> <u>F M L</u>	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	19 Nov 85 ddmmmyy	21 Nov 85 ddmmmyy	23 Nov 85 ddmmmyy	26 Nov 85 ddmmmyy	29 Nov 85 ddmmmyy
NA: 135-148 MEQ/L	143	144	141	139	
K: 3.5-5.0 MEQ/L	4.2	4.2	3.6	4.0	
CL: 96-109 MEQ/L	106	104	107	108	
CO2: 24-30 MEQ/L	28	24	21	26	
SUN: 12-25 MG/DL	8	11	10	10	
CREAT: 0.4-1.5 MG/DL	0.9	0.9	1.0	0.9	
GLU: 70-115 MG/DL	88	91	120	88	
T. BILI: 0.3-1.2 MG/DL	0.6	0.9	1.0	0.6	
D. BILI: 0.1-0.4 MG/DL	0.1	0.1	0.1	0.1	
CA: 9.0-11.0 MG/DL	10.4	10.0	9.8	9.6	
PO4: 3.0-4.5 MG/DL	3.7	4.2	3.8	4.1	
URIC A: 4.2-8.8 MG/DL	6.1	5.9	6.0	5.6	
T. PROT: 6.0-8.5 G/DL	7.4	7.4	6.9	6.6	
ALB.: 3.2-5.3 G/DL	5.1	4.9	4.4	4.1	
AST: 0-35 IU/L	17	17	12	14	
ALT: 0-30 IU/L	16	11	12	14	
ALK PHOS: 0-95 IU/L	64	68	58	57	
CHOL: 151-268 MG/DL	197	ND	ND	ND	
LDH: 0-200 IU/L	ND	116	99	105	
CPK: 0-160 U/L (male)	ND	153	100	90	110

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{E}{F} \frac{M}{M} \frac{K}{L}$	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	19 Nov 85 ddmmmyy	21 Nov 85 ddmmmyy	23 Nov 85 ddmmmyy	26 Nov 85 ddmmmyy	----- ddmmmyy	Date
Hgb	13.9-16.3	15.0	15.1	14.6	14.3		
PCV	41.0-53.0	45.3	44.8	43.3	42.6		
Plt	150-350	288	270	274	282		
RBC	4.50-5.90	4.93	4.95	4.73	4.63		
WBC	4500-11000	4800	6200	3700	4200		
Bands	2-6%	0	5	1	5		
Polys	31-76%	54	70	56	59		
Eos	1-4%	1	1	3	3		
Bas		0	0	3	0		
Lymphs	24-44%	38	24	36	27		
Atyp Lym		0	0	0	0		
Monos	2-11%	7	0	3	6		
Other		0	0	0	0		
Retics	0.5-1.5%	N.D.	1.2	1.2	1.7		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{matrix} E & M & K \\ F & M & L \end{matrix}$	05	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

University of Illinois at Chicago
Johns Hopkins Hospital
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	20 Nov 85 ddmmmyy	22 Nov 85 ddmmmyy	25 Nov 85 ddmmmyy	26 Nov 85 ddmmmyy	----- ddmmmyy	Date
Color/Sp		ND	ND	ND	ND		
Sp. Gr.		1.015	1.018	1.015	1.023		
pH		6.5	6.0	6.5	6.0		
Protein		Trace	Neg	Neg	Neg		
Ketones		neg	Neg	Neg	Neg		
Occ Bld		neg	Neg	Neg	Neg		
Bili.		neg	Neg	Neg	Neg		
RBC		0	rare	0	rare		
WBC		0	rare	0	rare		
Casts		0	0	0	0		
Epi. Cel		0	0	0	0		
Crystals		0	0	0	0		
Bacteria		0	0	0	0		
					a lot of amorphous material		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
20 Nov 85	✓		
23 Nov 85	✓		
26 Nov 85	✓		axis shifted from 0° to 15°

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E m k</u> F M L	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>--</u> <u>K</u> F M L	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	21 Nov 85	Screening laboratory
—	21 Nov 85	History, Physical Exam
0	21 Nov 85	Admission
2	22 Nov 85	P.O.
5	25 Nov 85	I.V.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 06.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Pitter M.D.
Investigator's signature

24, Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> F M L	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 21/Nov/85
dd mmm yy

Examiner Brent G. Petty MD

Date of birth 24/MAR/59
dd mmm yy

Brent G. Petty
print name

Age 26 yrs

Sex M

Race W
Fr

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	
Alcohol Use	✓		Quit 1 1/2 yrs ago
Recreational Drug Use	✓		Smoked MJ
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	"Pharm-kinetics" 3/85 Interferon 9/85 Ceftazidime 1984
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	dog "dipped" at veterinarian ~3 months ago + "dog soap" before that
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	R -- K F M L	06	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 21/NOV/85
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4 c</u>	<u>78/min</u>	<u>18/min</u>	<u>118/76</u>	<u>171.0</u>	<u>52.2</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			N.D.
Rectal			N.D.
Extremities	✓		
Skin		✓	Tattoos (R) upper arm, (L) upper arm, (L) forearm, (L) hand
Neurologic	✓		hyporeflexic diffusely

CHEST X-RAY

Date 05/AUG/85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{K}{M} \frac{L}{L}$	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD**STUDY: IV PYRIDOSTIGMINE**

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0935	1005	IV	NA

syringe + syringe = 41.36160
 syringe dose = 21.40249

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>NG/ML</u>	RBC ACHe <u>uM/ml/min</u>
B01, B47	0	25 Nov 85	0810	0810	B01: *	B47: 14.26
B02	0.08	"	0940	0940	B02: 17.0	
B03	0.16	"	0945	0945	B03: 19.9	
B04, B48	0.25	"	0950	0950	B04: 29.5	B48: 11.01
B05	0.33	"	0955	0955	B05: 28.2	
B06	0.42	"	1000	1000	B06: 34.8	
B07, B49	0.50	"	1005	1005	B07: 35.3	B49: 9.65
B08	0.58	"	1010	1010	B08: 20.4	
B09	0.66	"	1015	1015	B09: 11.9	
B10, B50	0.75	"	1020	1020	B10: 10.1	B50: 9.45
B11	0.83	"	1025	1025	B11: 9.91	
B12	0.92	"	1030	1030	B12: 7.60	
B13, B51	1.0	"	1035	1035	B13: 7.18	B51: 10.47
B14, B52	1.33	"	1055	1055	B14: 2.98	B52: 10.93
B15, B53	1.66	"	1115	1115	B15: 2.02	B53: 11.46
B16, B54	2.0	"	1135	1135	B16: 2.09	B54: 11.94
B17	2.5	"	1205	1205	B17: 1.90	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	R -- K F M L	06	Pyridostigmine
			PROTOCOL
			DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0935	1005	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	25 Nov 85	1235	1235	B18: 3.20	B55: 13.45
B19	3.5	"	1305	1305	B19: 2.53	
B20, B56	4.0	"	1335	1405	B20: *	B56: 13.11
B21	5.0	"	1435	1435	B21: *	
B22, B57	6.0	"	1535	1535	B22: *	B57: 14.42
B23	7.0	"	1635	1635	B23: *	
B24	8.0	"	1735	1735	B24: *	
B25	10.0	"	1935	1935	B25: *	
B26	12.0	"	2135	2135	B26: *	
B27, B58	24.0	26 Nov 85	0935	0935	B27: *	B58: 14.37

* below assay sensitivity 216

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	R -- K F M L	06	Pyridostigmine DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 85	0935	1005	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	25 Nov 85	0810	0810	# 76	# 39/44	# ck
	0.8	"	0940	0940			
	0.16	"	0945	0945			
	0.25	"	0950	0950	# 72		
	0.33	"	0955	0955			
	0.42	"	1000	1000			
	0.50	"	1005	1005	# 74	# 42/39	# ck
	0.58	"	1010	1010			
	0.66	"	1015	1015			
	0.75	"	1020	1020	# 76	40/4	
	0.83	"	1025	1025		20	
	0.92	"	1030	1030			
	1.0	"	1035	1035	# 76	# 40/42	
	1.33	"	1055	1055	# 80		
	1.66	"	1115	1115	# 76		
	2.0	"	1135	1135	# 76	# 40/41	
	2.5	"	1205	1205			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{--}{M} \frac{K}{L}$	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	25 Nov 86	0935	1005	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	25 Nov 85	1235	1235	#74		
	3.5	"	1305	1305			
	4.0	"	1335	1405	#82	#42/45	
	5.0	"	1435	1435			
	6.0	"	1535	1535	#80	#45/39	
	7.0	"	1635	1635			
	8.0	"	1735	1735			
	10.0	"	1935	1935			
	12.0	"	2135	2135			
	24.0	26 Nov 85	0935	0935	#90	#44/46	#ok

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> -- <u>K</u> F M L	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 86	0855	0855	PO	NA

syringe + pyridox = 6.73128
 syringe alone = 4.63942

DOSAGE (total) 20 mg.**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	22 Nov 86	0819	0819	B28: *	B59: 14.86
B29, B60	0.25	"	0910	0910	B29: 4.75	B60: 14.04
B30, B61	0.50	"	0925	0925	B30: 8.94	B61: 13.19
B31, B62	0.75	"	0940	0940	B31: 13.8	B62: 11.38
B32, B63	1.0	"	0955	0955	B32: 14.7	B63: 11.98
B33, B64	1.33	"	1015	1015	B33: 14.4	B64: 11.13
B34, B65	1.66	"	1035	1035	B34: 14.5	B65: 10.58
B35, B66	2.0	"	1055	1055	B35: 10.6	B66: 10.93
B36	2.5	"	1125	1125	B36: 10.8	
B37, B67	3.0	"	1155	1155	B37: 10.5	B67: 11.26
B38	3.5	"	1225	1225	B38: 9.33	
B39, B68	4.0	"	1255	1257	B39: 8.24	B68: 10.98
B40	5.0	"	1355	1355	B40: 4.55	
B41, B69	6.0	"	1455	1455	B41: 3.79	B69: 13.34
B42	7.0	"	1555	1555	B42: 3.62	
B43 B69A	8.0	"	1655	1655	B43: 3.36	B69A: 13.74
B44	10.0	"	1855	1855	B44: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{array}{cc} R & K \\ \hline F & M \\ & L \end{array}$	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0855	0855	PO	NA

DOSAGE (total) 20 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 220

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> -- <u>K</u> F M L	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	22 Nov 85	0855	0855	PO	NA

DOSAGE (total) 20 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	22 Nov 85	0819	0819	#84	#44/45	# ok
	0.25	"	0910	0910	#77		
	0.50	"	0925	0925	#63	#41/42	# ok
	0.75	"	0940	0940	#72		
	1.0	"	0955	0955	#65	#41/49	
	1.33	"	1015	1015	#69		
	1.66	"	1035	1035	#70		
	2.00	"	1055	1055	#75	#33/44	
	2.5	"	1125	1125			
	3.0	"	1155	1155	#79		
	3.5	"	1225	1225			
	4.0	"	1255	1257	#68	#45/42	
	5.0	"	1355	1355			
	6.0	"	1455	1455	#80	#38/40	
	7.0	"	1555	1555			
	8.0	"	1655	1655			
	10.0	"	1855	1855			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>JB</u> -- <u>K</u> F M L	<u>06</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory JHHJohns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NO</u> ddmmmyy	<u>21 Nov 85</u> ddmmmyy	<u>23 Nov 85</u> ddmmmyy	<u>26 Nov 85</u> ddmmmyy	Date
NA: 135-148 MEQ/L		146	142	140	
K: 3.5-5.0 MEQ/L		4.1	3.7	4.1	
CL: 96-109 MEQ/L		109	106	108	
CO2: 24-30 MEQ/L		25	24	24	
SUN: 12-25 MG/DL		15	10	11	
CREAT: 0.4-1.5 MG/DL		1.0	1.0	0.8	
GLU: 70-115 MG/DL		82	160	72	
T. BILI: 0.3-1.2 MG/DL		0.0	0.5	0.3	
D. BILI: 0.1-0.4 MG/DL		0.1	0.1	0.0	
CA: 9.0-11.0 MG/DL		9.6	9.5	9.9	
PO4: 3.0-4.5 MG/DL		4.4	2.7	3.5	
URIC A: 4.2-8.8 MG/DL		5.7	6.1	5.5	
T. PROT: 6.0-8.5 G/DL		7.1	6.8	6.8	
ALB.: 3.2-5.3 G/DL		4.9	4.5	4.9	
AST: 0-35 IU/L		15	13	15	
ALT: 0-30 IU/L		7	10	8	
ALK PHOS: 0-95 IU/L		74	62	65	
CHOL: 151-268 MG/DL		N.D.	N.D.	N.D.	
LDH: 0-200 IU/L		118	107	N.D.	
CPK: 0-160 U/L (male)		51	49	N.D.	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{K}{L}$ M	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	<u>N.D.</u> ddmmmyy	<u>21 Nov 85</u> ddmmmyy	<u>23 Nov 85</u> ddmmmyy	<u>26 Nov 85</u> ddmmmyy	_____ Date ddmmmyy
Hgb	13.9-16.3		16.3	15.6	14.6	
PCV	41.0-53.0		49.1	45.4	44.0	
Plt	150-350		289	263	307	
RBC	4.50-5.90		5.63	5.29	5.08	
WBC	4500-11000		7300	5700	6900	
Bands	2-6%		9	7	6	
Polys	31-76%		66	51	76	
Eos	1-4%		5	1	1	
Bas			1	1	0	
Lymphs	24-44%		14	28	14	
Atyp Lym			0	0	0	
Monos	2-11%		5	11	3	
Other			0	0	0	
Retics	0.5-1.5%		0.8	0.9	N.D	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{K}{L}$ M	06	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University
Johns Hopkins Hospital
Clinical Pharmacology*

TEST	NORMAL	Screen			Predrug		Study Date
		ddmmyy	21 Nov 85 ddmmyy	25 Nov 85 ddmmyy	26 Nov 85 ddmmyy	ddmmyy	
Color/Sp			ND	ND	ND		
Gr.			1.022	1.020	1.017		
pH			6.0	6.0	6.0		
Protein			Trace	Trace	Neg		
Ketones			Neg	neg	Neg		
Occ Bld			Neg	neg	Neg		
Bili.			Neg	neg	Neg		
RBC			0	0	0		
WBC			0	0	0		
Casts			0	0	0		
Epi. Cel			0	0	0		
Crystals			0-4	0	0		
Bacteria			0	0	0		

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
21 Nov 85	✓		
23 Nov 85	✓		
26 Nov 85	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> F M L	<u>06</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I</u> <u>-</u> <u>I</u> <u>F</u> <u>M</u> <u>L</u>	<u>07</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
<u>—</u>	<u>02 JAN 86</u>	Screening laboratory
<u>—</u>	<u>03 JAN 86</u>	History, Physical Exam
<u>0</u>	<u>05 JAN 86</u>	Admission
<u>2</u>	<u>06 JAN 86</u>	<u>P.O.</u>
<u>5</u>	<u>09 JAN 86</u>	<u>I.V.</u>

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 07.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>T</u> F <u>M</u> <u>L</u>	<u>07</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation

03 JAN
01/03/86
dd mm yy

Examiner

Brent G. Petty, MD
Brent G. Petty
print name

Date of birth

01 JUN
06/01/57
dd mm yy

Age

28
yrs

Sex

M

Race

B

No Yes Comments

Allergy	✓		
Tobacco Use	✓		
Alcohol Use	✓		
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Tobramycin
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC, 1st pills, resolved
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Pesticide at home months ago.
Other		✓	Schile trait

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I - I</u> <u>F M L</u>	<u>07</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/03/86
 21 dd mm yy
 03 JAN

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4</u> C	<u>72</u> min	<u>20</u> min	<u>118/68</u>	<u>171.0</u>	<u>80.5</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Mild scleritis @ rim, few conjunctival excoriations pt. <u>pharynx</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		ND	
Rectal		ND	
Extremities	✓		
Skin		✓	Scars @ eyebrow, ant. dist. @ forearm, @ ant. thorax. Arteriovenous @ upper arm
Neurologic	✓		

CHEST X-RAY

Date 03/JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty, MD
Brent G. Petty, M.D.
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{I}{F} - \frac{I}{M} - \frac{I}{L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09JAN86	0820	0850	IV	NA

Syringe + syringe = 42.74206 g DOSAGE (total) 1.32 mg.
 syringe - syringe = 22.68077 g

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	09JAN86	0815	0815	B01:*	B47:10.06
B02	0.08	"	0825	0825	B02:8.51	
B03	0.16	"	0830	0830	B03:13.8	
B04, B48	0.25	"	0835	0835	B04:18.4	B48:8.20
B05	0.33	"	0840	0840	B05:15.6	
B06	0.42	"	0845	0845	B06:16.3	
B07, B49	0.50	"	0850	0850	B07:17.9	B49:7.12
B08	0.58	"	0855	0855	B08:13.0	
B09	0.66	"	0900	0900	B09:10.1	
B10, B50	0.75	"	0905	0905	B10:9.95	B50:7.47
B11	0.83	"	0910	0910	B11:7.65	
B12	0.92	"	0915 0920	0915	B12:6.16	
B13, B51	1.0	"	0920 0940	0920	B13:6.34	B51:7.79
B14, B52	1.33	"	0940 1000	0940	B14:4.14	B52:8.27
B15, B53	1.66	"	1000 1020	1000	B15:2.86	B53:8.55
B16, B54	2.0	"	1020	1020	B16:2.58	B54:8.80
B17	2.5	"	1050	1050	B17:2.71	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	F - I F M L	07	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09JAN86	0820	0850	IV	N/A

DOSAGE (total)

1.32 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	09JAN86	1120	1120	B18: 1.95	B55: 9.23
B19	3.5	"	1150	1150	B19: 2.15	
B20, B56	4.0	"	1220	1220	B20: *	B56: 9.56
B21	5.0	"	1320	1320	B21: *	
B22, B57	6.0	"	1420	1420	B22: *	B57: 9.74
B23	7.0	"	1520	1520	B23: *	
B24	8.0	"	1620	1620	B24: *	
B25	10.0	"	1820	1820	B25: *	
B26	12.0	"	2020	2020	B26: *	
B27, B58	24.0	10JAN86	0820	0820	B27: *	B58: 10.30

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{T}{F} \frac{-}{M} \frac{T}{L}$	07	Pyridostigmine
			PROTOCOL
			DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09JAN86	0820	0850	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**N.B.: Hand grip meter not working reliably \bar{p} 100 cm 09JAN

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	09JAN86	0815	0815	#72	#53/55	# ok
	0.8	"	0825	0825			
	0.16	"	0830	0830			
	0.25	"	0835	0835	#70		
	0.33	"	0840	0840			
	0.42	"	0845	0845			
	0.50	"	0850	0850	#80	#58/54	# ok
	0.58	"	0855	0855			
	0.66	"	0900	0900			
	0.75	"	0905	0905	#70		
	0.83	"	0910	0910			
	0.92	"	0915	0915			
	1.0	"	0920	0920	#74	#59/56	
	1.33	"	0940	0940	#64		
	1.66	"	1000	1000	#72		
	2.0	"	1020	1020	#90	#45/48	
	2.5	"	1050	1050			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{array}{c} \overline{\text{I}} \\ \text{F} \end{array} \quad \begin{array}{c} \overline{\text{M}} \\ \text{M} \end{array} \quad \begin{array}{c} \overline{\text{Y}} \\ \text{L} \end{array}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09JAN86	0820	0850	IV	N/A

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{matrix} I & - & I \\ F & M & L \end{matrix}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	06 JAN 86	0855	0855	PO	NA

Syringe + pyrido = 7.12439 g

DOSAGE (total) 16.0 mg

Syringe - pyrido = 5.99580 g

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	06 JAN 86	0810	0810	B28: *	B59: 10.17
B29, B60	0.25	"	0910	0910	B29: *	B60: 9.94
B30, B61	0.50	"	0925	0925	B30: 6.43	B61: 9.05
B31, B62	0.75	"	0940	0940	B31: 8.24	B62: 8.79
B32, B63	1.0	"	0955	0955	B32: 8.33	B63: 8.48
B33, B64	1.33	"	1015	1015	B33: 8.69	B64: 8.27
B34, B65	1.66	"	1035	1035	B34: 12.3	B65: 7.46
B35, B66	2.0	"	1055	1055 1055	B35: 9.72	B66: 7.22
B36	2.5	"	1125	1125	B36: 9.63	
B37, B67	3.0	"	1155	1155	B37: 13.8	B67: 7.03
B38	3.5	"	1225	¹²²⁵ 1255	B38: 10.9	
B39, B68	4.0	"	1255	1255	B39: 8.48	B68: 7.53
B40	5.0	"	1355	1355	B40: 5.08	
B41, B69	6.0	"	1455	1455	B41: 2.69	B69: 8.59
B42	7.0	"	1555	1555	B42: 4.25	
B43	8.0	"	1655	1655	B43: *	B69A: 9.02
B44	10.0	"	1855	1855	B44: *	9.55

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{I}{F} - \frac{I}{M L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
02	06 JAN 86	0855	0855	PO	NA

DOSAGE (total) 16.0 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 235

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{array}{c} \text{I} \\ \text{F} \end{array} \quad \begin{array}{c} \text{--} \\ \text{M} \end{array} \quad \begin{array}{c} \text{I} \\ \text{L} \end{array}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
02	06 JAN 86	0855	0855	PO	NA

DOSAGE (total) 16.0 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	06 JAN 86	0810	0810	#64	#51/59	#OK
	0.25	"	0910	0910	#60		
	0.50	"	0925	0925	#60	#43/51	#OK
	0.75	"	0940	0940	#58		
	1.0	"	0955	0955	#64	#46/59	
	1.33	"	1015	1015	#80		
	1.66	"	1035	1035	#64		
	2.00	"	1055	1055	#72	#45/51	
	2.5	"	1125	1125			
	3.0	"	1155	1155	#78		
	3.5	"	1225	1225			
	4.0	"	1255	1255	#80	#43/56	
	5.0	"	1355	1355			
	6.0	"	1455	1455	#78	#60/45	
	7.0	"	1555 1655	1555			
	8.0	"	1655 1755	1655			
	10.0	"	1855	1855			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I</u> F <u>M</u> <u>L</u>	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
02	06 JAN 86	0855	0855	PO	NA

DOSAGE (total)

16.0 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{T}{F} - \frac{T}{M} - \frac{T}{L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	02 JAN 85 ddmmmyy	05 JAN 85 ddmmmyy	06 JAN 85 ddmmmyy	07 JAN 85 ddmmmyy	08 JAN 85 ddmmmyy
NA: 135-148 MEQ/L	142	141		144	
K: 3.5-5.0 MEQ/L	3.9	4.3		4.2	
CL: 96-109 MEQ/L	103	104		110	
CO2: 24-30 MEQ/L	27	28		25	
SUN: 12-25 MG/DL	10	12		9	
CREAT: 0.4-1.5 MG/DL	1.0	1.1		0.7	
GLU: 70-115 MG/DL	77	81		83	
T. BILI: 0.3-1.2 MG/DL	2.5	1.2		1.0	
D. BILI: 0.1-0.4 MG/DL	0.2	0.1		0.1	
CA: 9.0-11.0 MG/DL	9.8	9.8		8.8	
PO4: 3.0-4.5 MG/DL	3.9	4.5		4.1	
URIC A: 4.2-8.8 MG/DL	6.8	6.5		ND	
T. PROT: 6.0-8.5 G/DL	7.2	7.1		6.4	
ALB.: 3.2-5.3 G/DL	5.0	4.9		4.3	
AST: 0-35 IU/L	2	14		13	
ALT: 0-30 IU/L	18	19		20	
ALK PHOS: 0-95 IU/L	46	44		40	
CHOL: 151-268 MG/DL	ND	ND		181	
LDH: 0-200 IU/L	ND	151	141	138	150
CPK: 0-160 U/L (male)	ND	218	155	123	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{I}{F} \quad \frac{-}{M} \quad \frac{I}{L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NA</u> ddmmmyy	<u>NA</u> ddmmmyy	<u>10 JAN 85</u> ddmmmyy	<u>ddmmmyy</u>	<u>ddmmmyy</u>	Date
NA: 135-148 MEQ/L			141			
K: 3.5-5.0 MEQ/L			4.1			
CL: 96-109 MEQ/L			105			
CO2: 24-30 MEQ/L			27			
SUN: 12-25 MG/DL			13			
CREAT: 0.4-1.5 MG/DL			1.1			
GLU: 70-115 MG/DL			80			
T. BILI: 0.3-1.2 MG/DL			0.9			
D. BILI: 0.1-0.4 MG/DL			0.1			
CA: 9.0-11.0 MG/DL			9.3			
PO4: 3.0-4.5 MG/DL			4.4			
URIC A: 4.2-8.8 MG/DL			5.8			
T. PROT: 6.0-8.5 G/DL			6.6			
ALB.: 3.2-5.3 G/DL			4.5			
AST: 0-35 IU/L			25			
ALT: 0-30 IU/L			36			
ALK PHOS: 0-95 IU/L			38			
CHOL: 151-268 MG/DL			178			
LDH: 0-200 IU/L			145			
CPK: 0-160 U/L (male)			136			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{I}{F} \quad \frac{-}{M} \quad \frac{I}{L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen		Predrug		Study	
		02 JAN 86	05 JAN 86	07 JAN 86	10 JAN 86	Date	
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy		
Hgb	13.9-16.3	14.9	14.5	13.7	13.1		
PCV	41.0-53.0	43.2	42.2	39.8	38.7		
Plt	150-350	227	224	197	223		
RBC	4.50-5.90	4.95	4.79	4.79	4.43		
WBC	4500-11000	5600	6200	4400	5600		
Bands	2-6%	8	10	14	7		
Polys	31-76%	61	52	54	54		
Eos	1-4%	0	0	1	2		
Bas		1	0	0	0		
Lymphs	24-44%	27	26	23	30		
Atyp Lym		0	2	0	0		
Monos	2-11%	3	10	8	7		
Other		0	0	0	0		
Retics	0.5-1.5%	ND	1.4	1.1	1.4		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{I}{F} \frac{-}{M} \frac{I}{L}$	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory Johns Hopkins University
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	03 JAN 86 ddmmmyy	05 JAN 86 ddmmmyy	07 JAN 86 ddmmmyy	10 JAN 86 ddmmmyy	_____ Date ddmmmyy
Color/Ap		clear	milky	clear	clear	
Sp. Gr.		1.019	1.021	1.024	1.023	
pH		5.0	5.0	6.0	6.0	
Protein		neg	traces	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		0	0	0	0	
Casts		0	0	0	0	
Epi. Cel		0	0	0	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
03 JAN 86	✓		
07 JAN 86	✓		
10 JAN 86	✓		not done

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I</u> <u>--</u> <u>I</u> F M L	07	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		____ _ dd mmm yy	____ _ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		____ _ dd mmm yy	____ _ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	<u>08</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	26 DEC 85	Screening laboratory
—	02 JAN 86	History, Physical Exam
0	05 JAN 86	Admission
2	06 JAN 86	P.O.
5	09 JAN 86	I.V.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 08.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O H W</u> F M L	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 02/JAN/86
dd mm yy

Examiner Brent G. Petty

Date of birth 10/OCT/50
dd mm yy

Brent G. Petty
print name

Age 35 yrs

Sex m

Race W

No Yes Comments

Allergy	✓		
Tobacco Use	✓		
Alcohol Use		✓	4 beers / wk
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	JHU
Blood or plasma donor	✓		
Prior Surgery		✓	1977 (1) hernia repair 1978 (1) wrist cystic resection 1979 (1) spinal fusion
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Exterminator at home 10 mos ago
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
<u>Lietman</u>	<u>Q M W</u> <u>F M L</u>	<u>08</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 02/JAN/86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.5 C</u>	<u>64/min</u>	<u>20/min</u>	<u>124/78</u>	<u>178.0</u>	<u>75.9</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Septum → <u>(R)</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			<u>N D</u>
Rectal			<u>N. D.</u>
Extremities	✓		
Skin		✓	<u>D. ffuse sl. raised prob. hyperplastic Follicles</u>
Neurologic	✓		

CHEST X-RAY

Date 02/JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O H W</u> <u>F M L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09JAN86	0813	0843	IV	N/A

Syringe + P = 42.54756

DOSAGE (total) 1.32 mg

syringe - P = 22.48720

PLASMA CONCENTRATIONS

NB: pump infusing too quickly for 1st 15 minutes

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	09JAN86	0812	0812	B01: *	B47: 13.16
B02	0.08	"	0818	0818	B02: 9.69	
B03	0.16	"	0823	0823	B03: 20.9	
B04, B48	0.25	"	0828	0828	B04: 18.9	B48: 10.31
B05	0.33	"	0833	0833	B05: 14.5	
B06	0.42	"	0838	0838	B06: 13.5	
B07, B49	0.50	"	0843	0843	B07: 11.7	B49: 9.45
B08	0.58	"	0848	0848	B08: 10.8	
B09	0.66	"	0853	0853	B09: 8.15	
B10, B50	0.75	"	0858	0858	B10: 5.82	B50: 10.28
B11	0.83	"	0903	0903	B11: 5.26	
B12	0.92	"	0908	0905	B12: 4.34	
B13, B51	1.0	"	0913	0913	B13: 3.51	B51: 10.85
B14, B52	1.33	"	0933	0933	B14: 3.37	B52: 11.56
B15, B53	1.66	"	0953	0953	B15: 2.75	B53: 11.99
B16, B54	2.0	"	1013	1013	B16: *	B54: 12.10
B17	2.5	"	1043	1043	B17: 1.59	

* below assay sensitivity 246

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09 JAN 82	0813	0843	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 247

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>Q H W</u> <u>F M L</u>	<u>08</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>09 JAN 86</u>	<u>0813</u>	<u>0843</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**NB: Hand grip meter stopped working accurately ~ 1000 hr

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	<u>0</u>	<u>09 JAN 86</u>	<u>0800</u> <u>0812</u>	<u>0812</u>	<u># 84</u>	<u># 47/44</u>	<u># ok</u>
	<u>0.8</u>	<u>"</u>	<u>0818</u>	<u>0818</u>			
	<u>0.16</u>	<u>"</u>	<u>0823</u>	<u>0823</u>			
	<u>0.25</u>	<u>"</u>	<u>0828</u>	<u>0828</u>	<u># 78</u>		
	<u>0.33</u>	<u>"</u>	<u>0833</u>	<u>0833</u>			
	<u>0.42</u>	<u>"</u>	<u>0838</u>	<u>0838</u>			
	<u>0.50</u>	<u>"</u>	<u>0843</u>	<u>0843</u>	<u># 88</u>	<u># 49/55</u>	<u># ok</u>
	<u>0.58</u>	<u>"</u>	<u>0848</u>	<u>0848</u>			
	<u>0.66</u>	<u>"</u>	<u>0853</u>	<u>0853</u>			
	<u>0.75</u>	<u>"</u>	<u>0858</u>	<u>0858</u>	<u># 82</u>		
	<u>0.83</u>	<u>"</u>	<u>0903</u>	<u>0903</u>			
	<u>0.92</u>	<u>"</u>	<u>0908</u>	<u>0905</u>			
	<u>1.0</u>	<u>"</u>	<u>0913</u>	<u>0913</u>	<u># 70</u>	<u># 53/43</u>	
	<u>1.33</u>	<u>"</u>	<u>0933</u>	<u>0933</u>	<u># 70</u>		
	<u>1.66</u>	<u>"</u>	<u>0953</u>	<u>0953</u>	<u># 70</u>		
	<u>2.0</u>	<u>"</u>	<u>1013</u>	<u>1013</u>	<u># 68</u>	<u># 31/36</u>	
	<u>2.5</u>	<u>"</u>	<u>1043</u>	<u>1043</u>		<u># 28</u>	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>Ω</u> <u>F</u> <u>H</u> <u>M</u> <u>L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	09 JAN 84	0813	0843	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{O}{F} \frac{H}{M} \frac{W}{L}$	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	06 JAN 86	0858	0858	PO	NA

syringe + pyrido = 7.62874g
 syringe 5 pyrido = 5.98388g

DOSAGE (total)

16 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	06 JAN 86	0805	0805	B28: *	B59: 13.63
B29, B60	0.25	"	0913	0913	B29: *	B60: 13.50
B30, B61	0.50	"	0928	0928	B30: 2.21	B61: 13.03
B31, B62	0.75	"	0943	0943	B31: 6.44	B62: 12.30
B32, B63	1.0	"	0958	0958	B32: 5.14	B63: 12.09
B33, B64	1.33	"	1018	1018	B33: 4.72	B64: 12.27
B34, B65	1.66	"	1038	1038	B34: 6.56	B65: 11.07
B35, B66	2.0	"	1058	1058	B35: 8.03	B66: 10.95
B36	2.5	"	1128	1128	B36: 7.15	
B37, B67	3.0	"	1158	1158	B37: 12.2	B67: 10.04
B38	3.5	"	1228	1228	B38: 9.30	
B39, B68	4.0	"	1258	1258	B39: 9.24	B68: 10.19
B40	5.0	"	1358	1358	B40: 4.96	
B41, B69	6.0	"	1458	1458	B41: 3.22	B69: 12.12
B42	7.0	"	1558	1558	B42: 2.24	
B43	8.0	"	1658	1658	B43: 1.80	B69A: 12.67
B44	10.0	"	1858	1858	B44: *	13.00

* below assay sensitivity 250

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>Q</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	<u>08</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	06 JAN 86	0858	0858	PO	NA

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O H W</u> <u>F M L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	06JAN86	0858	0858	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	06JAN86	0805		#88	#29/32	#OL
	0.25	"	0913		#90		-
	0.50	"	0928		#78	#41/45	#CL
	0.75	"	0943		#78		
	1.0	"	0958		#84	#37/45	
	1.33	"	1018		#76		
	1.66	"	1038		#72		
	2.00	"	1058		#64	#37/43	
	2.5	"	1128 1028				
	3.0	"	1158 1058		#76		
	3.5	"	1228				
	4.0	"	1258		#76	#38/41	
	5.0	"	1358				
	6.0	"	1458		#80	#33/42	
	7.0	"	1558 1658				
	8.0	"	1658 1758				
	10.0	"	1858				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>Q</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	06 JAN 88	0858	0858	PO	NA

DOSAGE (total) 16 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O H W</u> <u>F M L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>26 Dec 85</u> ddmmmyy	<u>05 JAN 86</u> ddmmmyy	<u>06 JAN 86</u> ddmmmyy	<u>07 JAN 86</u> ddmmmyy	<u>09 JAN 86</u> ddmmmyy	Date
NA: 135-148 MEQ/L	145	145		144		
K: 3.5-5.0 MEQ/L	5.0	4.9		4.7		
CL: 96-109 MEQ/L	108	104		104		
CO2: 24-30 MEQ/L	28	30		27		
SUN: 12-25 MG/DL	19	10		14		
CREAT: 0.4-1.5 MG/DL	0.9	1.0		0.9		
GLU: 70-115 MG/DL	93	108		79		
T. BILI: 0.3-1.2 MG/DL	0.4	0.5		0.5		
D. BILI: 0.1-0.4 MG/DL	0.0	0.1		0.0		
CA: 9.0-11.0 MG/DL	9.9	10.2		9.8		
PO4: 3.0-4.5 MG/DL	ND	4.1		4.3		
URIC A: 4.2-8.8 MG/DL	6.7	5.9		5.7		
T. PROT: 6.0-8.5 G/DL	7.2	7.1		7.3		
ALB.: 3.2-5.3 G/DL	4.8	5.0		5.0		
AST: 0-35 IU/L	23	15		17		
ALT: 0-30 IU/L	17	15		13		
ALK PHOS: 0-95 IU/L	54	49		49		
CHOL: 151-268 MG/DL	ND	ND		ND		
LDH: 0-200 IU/L	ND	122	200	131	119	
CPK: 0-160 U/L (male)	ND	66	49	41	61	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	NA ddmmyy	NA ddmmyy	10 JAN 86 ddmmyy	ddmmyy	ddmmyy	Date
NA: 135-148 MEQ/L			144			
K: 3.5-5.0 MEQ/L			4.9			
CL: 96-109 MEQ/L			105			
CO2: 24-30 MEQ/L			29			
SUN: 12-25 MG/DL			19			
CREAT: 0.4-1.5 MG/DL			1.0			
GLU: 70-115 MG/DL			85			
T. BILI: 0.3-1.2 MG/DL			0.3			
D. BILI: 0.1-0.4 MG/DL			0.0			
CA: 9.0-11.0 MG/DL			9.8			
PO4: 3.0-4.5 MG/DL			4.0			
URIC A: 4.2-8.8 MG/DL			6.6			
T. PROT: 6.0-8.5 G/DL			6.9			
ALB.: 3.2-5.3 G/DL			4.8			
AST: 0-35 IU/L			13			
ALT: 0-30 IU/L			11			
ALK PHOS: 0-95 IU/L			51			
CHOL: 151-268 MG/DL			215			
LDH: 0-200 IU/L			116			
CPK: 0-160 U/L (male)			56			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{O}{F} \frac{H}{M} \frac{W}{L}$	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen		Predrug		Study	
		26 Dec 85	05 JAN 86	07 JAN 86	10 JAN 86	Date	
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Hgb	13.9-16.3	15.0	15.4	15.0	13.8		
PCV	41.0-53.0	43.1	44.1	42.1	40.1		
Plt	150-350	273	298	276	301		
RBC	4.50-5.90	4.64	4.74	4.66	4.32		
WBC	4500-11000	7600	9200	7000	7800		
Bands	2-6%	10	9	8	4		
Polys	31-76%	54	69	59	75		
Eos	1-4%	4	1	2	2		
Bas		1	0	0	0		
Lymphs	24-44%	22	14	25	17		
Atyp Lym		6	1	0	0		
Monos	2-11%	3	6	6	2		
Other		0	0	0	0		
Retics	0.5-1.5%	ND	1.0	1.0	1.0		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O H W</u> <u>F M L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University of
Johns Hopkins Hospital
Clinical Pharmacology*

Screen Predrug

Study

TEST	NORMAL	02 JAN 86 ddmmyy	05 JAN 86 ddmmyy	07 JAN 86 ddmmyy	10 JAN 86 ddmmyy	----- ddmmyy	Date
Color/Sp		ND	yellow	yellow	clear		
Sp. Gr.		1.019	1.021	1.023	1.020		
pH		6.5	6.0	6.5	7.0		
Protein		neg	trace	neg	trace		
Ketones		neg	neg	neg	neg		
Occ Bld		neg	neg	neg	neg		
Bili.		neg	neg	neg	neg		
RBC		0	0	0	0		
WBC		0	0	0	0		
Casts		0	0	0	0		
Epi. Cel		0	0	0	0		
Crystals		0	0	0	0		
Bacteria		0	0	0	0		

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
02 JAN 86	✓		
07 JAN 86	✓		
10 JAN 86	✓		non-specific ST-T changes, questionably due to different machine.

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>O</u> <u>H</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		____ ____ ____ dd mmm yy ____ (0-2400)	____ ____ ____ dd mmm yy ____ (0-2400)	<input type="checkbox"/> Mild <input type="checkbox"/> Mod <input type="checkbox"/> Sev	<input type="checkbox"/> DEF. <input type="checkbox"/> PROB. <input type="checkbox"/> POSS. <input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> None <input type="checkbox"/> Treatment <input type="checkbox"/> Stop test drug
#		____ ____ ____ dd mmm yy ____ (0-2400)	____ ____ ____ dd mmm yy ____ (0-2400)	<input type="checkbox"/> Mild <input type="checkbox"/> Mod <input type="checkbox"/> Sev	<input type="checkbox"/> DEF. <input type="checkbox"/> PROB. <input type="checkbox"/> POSS. <input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> None <input type="checkbox"/> Treatment <input type="checkbox"/> Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J</u> F <u>R</u> M <u>S</u> L	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	26 DEC 85	Screening laboratory
—	26 DEC 85	History, Physical Exam
0	06 JAN 86	Admission
2	07 JAN 86	P.O.
5	10 JAN 86	I.V.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 09.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 26, Dec, 85
dd mm yy

Examiner Brent G. Petty, M.D.

Date of birth 05, JAN, 56
dd mm yy

Brent G. Petty, M.D.
print name

Age 29 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Tobacco Use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	1 pack per day
Alcohol Use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	2 cans beer/day on weekends
Recreational Drug Use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Marijuana 1 cigarette/month
Medications past 2 weeks	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Experimental Drug Exposure	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Pharmakinetico, FSK last 10/13/85
Blood or plasma donor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	last 1983
Prior Surgery	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Eye, ear, nose, throat	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Endocrine (diabetes, thyroid)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
C-V (heart murmur, HBP)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pulmonary (cough, asthma)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Hepatitis, gastro-intestinal	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Genito-urinary	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Musculoskeletal	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Neuropsychiatric	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pesticide/herbicide use	<input checked="" type="checkbox"/>	<input type="checkbox"/>	last exterminator visit 3 mos ago. No pets. No insecticide use.
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 26/Dec/85
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.2</u> C	<u>68</u> /min	<u>16</u> /min	<u>112/78</u>	<u>182.00</u>	<u>76.5</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Few lymphoid excrescences (R) posterior pharynx, fair dentition, mild gingivitis, pigmentation of gums.
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		ND	
Rectal		ND	
Extremities	✓		
Skin		✓	Scars (L) upper arm, (L) lower back, forehead, knees from MVA 1979
Neurologic	✓		left handed

CHEST X-RAY

Date 20/Nov/85

NORMAL	✓	ABNORMAL		Describe abnormalities:
Small calcified granulomata in each apex.				

Examiner

Brent G. Petty, M.D.

Brent G. Petty, M.D.
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	09	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0940	1005	IV	N/A

Syringe + pyrido = 42.74748
Syringe - pyrido = 22.65576

- Infusion faster than scheduled
2° pump going too fast
initially, then was slowed down.

DOSAGE (total)

1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	10 JAN 86	0940	0940	B01: N.R.	B47: 13.35
B02	0.08	"	0945	0945	B02: 4.75	
B03	0.16	"	0950	0950	B03: 8.73	
B04, B48	0.25	"	0955	0955	B04: 13.6	B48: 11.48
B05	0.33	"	1000	1000	B05: 25.9	
B06	0.42	"	1005	1005	B06: 18.3	
B07, B49	0.50	"	1010	1010	B07: 20.3	B49: 9.70
B08	0.58	"	1015	1016	B08: 14.0	
B09	0.66	"	1020	1020	B09: 9.24	
B10, B50	0.75	"	1025	1025	B10: 9.19	B50: 9.53
B11	0.83	"	1030	1030	B11: 6.29	
B12	0.92	"	1035	1035	B12: 2.63	
B13, B51	1.0	"	1040	1040	B13: 6.27	B51: 10.34
B14, B52	1.33	"	1100	1100	B14: 4.04	B52: 10.51
B15, B53	1.66	"	1120	1120	B15: 1.81	B53: 11.05
B16, B54	2.0	"	1140	1140	B16: 2.38	B54: 11.55
B17	2.5	"	1210	1210	B17: 2.21	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J R S F M L	09	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0940	1005	IV	N/A

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	10 JAN 86	1240	1240	B18: *	B55: 12.04
B19	3.5	"	1310	1310	B19: *	
B20, B56	4.0	"	1340	1340	B20: *	B56: 12.54
B21	5.0	"	1440	1440	B21: *	
B22, B57	6.0	"	1540	1540	B22: *	B57: 13.18
B23	7.0	"	1640	1640	B23: *	
B24	8.0	"	1740	1740	B24: *	
B25	10.0	"	1940	1940	B25: *	
B26	12.0	"	2140	2140	B26: *	
B27, B58	24.0	11 JAN 86	0940	0940	B27: *	B58: 12.78

* Below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J R S F M L	09	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD**STUDY: IV PYRIDOSTIGMINE**

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0940	1005	IV	N/A

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

NB. Electronic handgrip meter not accurate on this day.

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R KG	Coord Test
	0	10 JAN 86	0940	0940	# 70	# 22/22	# OK
	0.8	"	0945	0945		22	
	0.16	"	0950	0950			
	0.25	"	0955	0955	# 70		
	0.33	"	1000	1000			
	0.42	"	1005	1005			
	0.50	"	1010	1010	# 76	# 24/24	# OK
	0.58	"	1015	1016		22	
	0.66	"	1020	1020			
	0.75	"	1025	1025	# 60		
	0.83	"	1030	1030			
	0.92	"	1035	1035			
	1.0	"	1040	1040	# 60	# 21/22	
	1.33	"	1100	1100	# 68	22	
	1.66	"	1120	1120	# 80		
	2.0	"	1140	1140	# 78	# 23/24	
	2.5	"	1210	1210		22	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{J}{F} \frac{R}{M} \frac{S}{L}$	09	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0940	1005	IV	N/A

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R KG	Coord Test
	3.0	10 JAN 86	1240	1240	# 72		
	3.5	"	1310	1310			
	4.0	"	1340	1340	# 80	# 21/21	
	5.0	"	1440	1440			
	6.0	"	1540	1540	# 84	# 23/25	
	7.0	"	1640	1640		21	
	8.0	"	1740	1740			
	10.0	"	1940	1940			
	12.0	"	2140	2140			
	24.0	11 JAN 86	0940	0940	# 84	# 21/20	# OK
						21	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>2</u>	<u>07 JAN 86</u>	<u>0840</u>	<u>0840</u>	<u>PO</u>	<u>N/A</u>

Syringe + pyrido = 7.63517

Syringe - pyrido = 5.95228

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	<u>07 JAN 86</u>	<u>0811</u>	<u>0811</u>	B28: *	B59: <u>12.76</u>
B29, B60	0.25	"	<u>0855</u>	<u>0855</u>	B29: *	B60: <u>12.38</u>
B30, B61	0.50	"	<u>0910</u>	<u>0910</u>	B30: <u>2.27</u>	B61: <u>12.03</u>
B31, B62	0.75	"	<u>0925</u>	<u>0925</u>	B31: <u>3.95</u>	B62: <u>11.51</u>
B32, B63	1.0	"	<u>0940</u>	<u>0940</u>	B32: <u>4.01</u>	B63: <u>11.35</u>
B33, B64	1.33	"	<u>1000</u>	<u>1000</u>	B33: <u>5.46</u>	B64: <u>11.02</u>
B34, B65	1.66	"	<u>1020</u>	<u>1020</u>	B34: <u>6.01</u>	B65: <u>10.91</u>
B35, B66	2.0	"	<u>1040</u>	<u>1040</u>	B35: <u>4.91</u>	B66: <u>10.59</u>
B36	2.5	"	<u>1110</u>	<u>1110</u>	B36: <u>4.76</u>	
B37, B67	3.0	"	<u>1140</u>	<u>1140</u>	B37: <u>4.21</u>	B67: <u>10.35</u>
B38	3.5	"	<u>1210</u>	<u>1210</u>	B38: <u>5.00</u>	
B39, B68	4.0	"	<u>1240</u>	<u>1240</u>	B39: <u>6.19</u>	B68: <u>9.98</u>
B40	5.0	"	<u>1340</u>	<u>1340</u>	B40: <u>6.65</u>	
B41, B69	6.0	"	<u>1440</u>	<u>1440</u>	B41: <u>2.11</u>	B69: <u>10.94</u>
B42	7.0	"	<u>1540</u>	<u>1548</u>	B42: <u>1.75</u>	
B43	8.0	"	<u>1640</u>	<u>1640</u>	B43: *	B69A: <u>11.71</u>
B44	10.0	"	<u>1840</u>	<u>1840</u>	B44: *	<u>11.78</u>

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{J}{F} \frac{R}{M} \frac{5}{L}$	09	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	07 JAN 86	0840	0840	PO	N/A

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	07 JAN 86	0802	0802	# 64	# 55/54	# OK
	0.25	"	0855	0855	# Not Done		-
	0.50	"	0910	0910	# 60	# 56/10	# OK
	0.75	"	0925	0925	# 64		
	1.0	"	0940	0940	# 64	# 59/53	
	1.33	"	1000	1000	# 58		
	1.66	"	1020	1020	# 48		
	2.00	"	1040	1040	# 62	# 49/49	
	2.5	"	1110	1110			
	3.0	"	1140	1140	# 60		
	3.5	"	1210	1210			
	4.0	"	1240	1240	# 64	# 56/59	
	5.0	"	1340	1340			
	6.0	"	1440	1440	# 70	# 57/54	
	7.0	"	1540	1548			
	8.0	"	1640	1640			
	10.0	"	1840	1840			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

TEST: NORMAL	Screen	Predrug	8 ^{am}	44 ^{pm}	Study
	26 Dec 85 ddmmyy	06 JAN 86 ddmmyy	07 JAN 86 ddmmyy	08 JAN 86 ddmmyy	09 JAN 86 ddmmyy
NA: 135-148 MEQ/L	143	141	138	139	
K: 3.5-5.0 MEQ/L	4.1	4.7	4.3	4.6	
CL: 96-109 MEQ/L	111	104	107	105	
CO2: 24-30 MEQ/L	28	28	21	25	
SUN: 12-25 MG/DL	18	13	14	18	
CREAT: 0.4-1.5 MG/DL	1.2	1.2	1.4	1.3	
GLU: 70-115 MG/DL	74	68	70	82	
T. BILI: 0.3-1.2 MG/DL	0.4	0.3	0.9	0.7	
D. BILI: 0.1-0.4 MG/DL	0.1	0.1	0.1	0.1	
CA: 9.0-11.0 MG/DL	9.2	9.9	9.5	10.2	
PO4: 3.0-4.5 MG/DL	ND	2.8	3.8	4.1	
URIC A: 4.2-8.8 MG/DL	5.1	4.5	5.1	5.4	
T. PROT: 6.0-8.5 G/DL	6.9	7.0	ND	ND	
ALB.: 3.2-5.3 G/DL	4.1	4.3	4.5	4.5	
AST: 0-35 IU/L	26	18	24	20	
ALT: 0-30 IU/L	16	13	16	13	
ALK PHOS: 0-95 IU/L	64	59	65	64	
CHOL: 151-268 MG/DL	ND	ND	197	210	
LDH: 0-200 IU/L	175	195	224	170	
CPK: 0-160 U/L (male)	ND	55 385	341	270	325

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J R S F M L	09	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	NA ddmmyy	NA ddmmyy	10 JAN 86 ddmmyy	11 JAN 86 ddmmyy	Date
NA: 135-148 MEQ/L				138	
K: 3.5-5.0 MEQ/L				4.0	
CL: 96-109 MEQ/L				105	
CO2: 24-30 MEQ/L				24	
SUN: 12-25 MG/DL				16	
CREAT: 0.4-1.5 MG/DL				1.3	
GLU: 70-115 MG/DL				104	
T. BILI: 0.3-1.2 MG/DL				0.4	
D. BILI: 0.1-0.4 MG/DL				0.1	
CA: 9.0-11.0 MG/DL				9.5	
PO4: 3.0-4.5 MG/DL				3.5	
URIC A: 4.2-8.8 MG/DL				5.1	
T. PROT: 6.0-8.5 G/DL				7.4	
ALB.: 3.2-5.3 G/DL				4.3	
AST: 0-35 IU/L				27	
ALT: 0-30 IU/L				26	
ALK PHOS: 0-95 IU/L				65	
CHOL: 151-268 MG/DL				205	
LDH: 0-200 IU/L				168	
CPK: 0-160 U/L (male)			257	264	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

		Screen	Predrug	Study		
		Date				
TEST	NORMAL	<u>26 Dec 85</u> ddmmmyy	<u>06 JAN 86</u> ddmmmyy	<u>07 JAN 86</u> ddmmmyy	<u>08 JAN 86</u> ddmmmyy	<u>11 JAN 86</u> ddmmmyy
Hgb	13.9-16.3	15.1	15.7	16.4	16.0	15.2
PCV	41.0-53.0	44.2	44.9	48.7	47.7	45.1
Plt	150-350	229	226	232	243	238
RBC	4.50-5.90	4.82	4.89	5.37	5.22	4.95
WBC	4500-11000	7400	9400	6500	6900	7200
Bands	2-6%	4	6	8	4	8
Polys	31-76%	64	71	43	53	58
Eos	1-4%	5	2	5	3	1
Bas		0	0	1	1	1
Lymphs	24-44%	17	15	32	26	24
Atyp Lym		0	0	0	1	0
Monos	2-11%	10	6	11	12	8
Other		0	0	0	0	0
Retics	0.5-1.5%	1.2	1.5	0.7	0.5	0.7

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{T}{F} \frac{R}{M} \frac{S}{L}$	09	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University of Maryland
Johns Hopkins Hospital
Clinical Pharmacology*

Screen: Predrug

Study

TEST	NORMAL	26 Dec 85 ddmmmyy	06 JAN 86 ddmmmyy	08 JAN 86 ddmmmyy	10 JAN 86 ddmmmyy	_____ Date ddmmmyy
Color/Ap		ND	yellow	cloudy	clear	
Sp. Gr.		1.018	1.023	1.021	1.021	
pH		6.5	6.5	6.0	6.0	
Protein		neg	- neg	neg	trace	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		0	0	0	0	
Casts		0	0	0	0	
Epi. Cel		0	0	0	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
02 JAN 86	✓		
08 JAN 86	✓		axis shifted rightward
11 JAN 86	✓		axis shifted leftward toward original

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R S</u> <u>F M L</u>	<u>09</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	02 JAN 86	Screening laboratory
—	02 JAN 86	History, Physical Exam
0	06 JAN 86	Admission
2	07 JAN 86	P.O.
5	10 JAN 86	IV

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 010.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> <u>F M L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 02, JAN, 86
dd mmm yy

Examiner Brent G. Petty M.D.

Date of birth 27, AUG, 54
dd mmm yy

print name

Age 31 yrs

Sex M

Race B

No Yes Comments

Allergy	✓		
Tobacco Use	✓		
Alcohol Use	✓		
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Pharmacokinetics - last n 2 mos ago University - last n 3 mos ago
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Dog washed for fleas n 1 month ago at his place. residence but he did not do the washing. Extermination last done n 6 mos. ago.
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>H</u> <u>M</u> <u>F</u> <u>M</u> <u>L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 02, JAN, 86

dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.5</u> c	<u>112</u> ^{excess} /min	<u>16</u> /min	<u>110</u> / <u>70</u>	<u>174.0</u>	<u>77.0</u>

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Uvula asymmetric and deviated to left
Chest, lungs	✓		
Heart	✓		Soft short systolic flow murmur
Abdomen	✓		
Genitalia		ND	
Rectal		ND	
Extremities	✓		
Skin		✓	Tattoo ® Forearm, scars ® anterolateral chest
Neurologic	✓		

CHEST X-RAY

Date 02, JAN, 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty, M.D.
BRENT G. Petty, M.D.
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> <u>F M L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>10 JAN 86</u>	<u>0950</u>	<u>1020</u>	<u>IV</u>	<u>N/A</u>

Syringe + pyrido = 42.44876
 Syringe - pyrido = 22.43366

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	<u>10 JAN 86</u>	<u>0945</u>	<u>0945</u>	B01: *	B47: <u>12.04</u>
B02	0.08	"	<u>0955</u>	<u>0955</u>	B02: <u>2.27</u>	
B03	0.16	"	<u>1000</u>	<u>1000</u>	B03: <u>5.23</u>	
B04, B48	0.25	"	<u>1005</u>	<u>1005</u>	B04: <u>3.94</u>	B48: <u>10.39</u>
B05	0.33	"	<u>1010</u>	<u>1010</u>	B05: <u>6.06</u>	
B06	0.42	"	<u>1015</u>	<u>1015</u>	B06: <u>9.61</u>	
B07, B49	0.50	"	<u>1020</u>	<u>1020</u>	B07: <u>12.4</u>	B49: <u>8.93</u>
B08	0.58	"	<u>1025</u>	<u>1025</u>	B08: <u>7.46</u>	
B09	0.66	"	<u>1030</u>	<u>1030</u>	B09: <u>5.32</u>	
B10, B50	0.75	"	<u>1035</u>	<u>1035</u>	B10: <u>4.78</u>	B50: <u>9.37</u>
B11	0.83	"	<u>1040</u>	<u>1040</u>	B11: <u>3.68</u>	
B12	0.92	"	<u>1045</u>	<u>1045</u>	B12: <u>2.99</u>	
B13, B51	1.0	"	<u>1050</u>	<u>1050</u>	B13: <u>2.81</u>	B51: <u>9.98</u>
B14, B52	1.33	"	<u>1110</u>	<u>1110</u>	B14: <u>1.62</u>	B52: <u>10.09</u>
B15, B53	1.66	"	<u>1130</u>	<u>1130</u>	B15: *	B53: <u>10.38</u>
B16, B54	2.0	"	<u>1150</u>	<u>1150</u>	B16: *	B54: <u>10.84</u>
B17	2.5	"	<u>1220</u>	<u>1220</u>	B17: *	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	W H M F M L	010	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0950	1020	IV	N/A

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	10 JAN 86	1250	1250	B18: *	B55: 10.90
B19	3.5	"	1320	1320	B19: *	
B20, B56	4.0	"	1350	1350	B20: *	B56: 11.57
B21	5.0	"	1450	1450	B21: *	
B22, B57	6.0	"	1550	1550	B22: *	B57: 12.30
B23	7.0	"	1650	1650	B23: *	
B24	8.0	"	1750	1750	B24: *	
B25	10.0	"	1950	1950	B25: *	
B26	12.0	"	2150	2150	B26: *	
B27, B58	24.0	11 JAN 86	0950	0950	B27: *	B58: 12.52

* below assay sensitivity 279

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0950	1020	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

NB: Electronic hand grip meter not working accurately on this date.

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	10 JAN 86	0945	0945	#80	#22/20	# OK
	0.8					20	
	0.16						
	0.25	"	1005	1005	#84		
	0.33						
	0.42						
	0.50	"	1020	1020	#78	#22/21	# OK
	0.58					20	
	0.66						
	0.75	"	1035	1035	#80		
	0.83						
	0.92						
	1.0	"	1050	1050	#72	#24/23	
	1.33	"	1110	1110	#88	20	
	1.66	"	1130	1130	#80		
	2.0	"	1150	1150	#70	#25/22	
	2.5					20	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	10 JAN 86	0950	1020	IV	N/A

DOSAGE (total) 1.32mg.

PHYSIOLOGIC VARIABLES

page 2

Sample No.	Scheduled Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	10 JAN 86	1250	1250	#70		
	3.5						
	4.0	10 JAN 86	1350	1350	#74	#23/25	
	5.0					LA	
	6.0	10 JAN 86	1550	1550	#80	#26/23	
	7.0					LA	
	8.0						
	10.0						
	12.0						
	24.0 (S)	11 JAN 86	0950	0950	#60	#24/19	# OK
						LA	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	07 JAN 86	0843	0843	PO	N/A

Syringe + pyrido = 7.62954
 Syringe - pyrido = 5.95975

DOSAGE (total)

1.6 mg.**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	07 JAN 86	0815	0815	B28: *	B59: 11.31
B29, B60	0.25	"	0858	0858	B29: *	B60: 11.02
B30, B61	0.50	"	0913	0913	B30: *	B61: 10.70
B31, B62	0.75	"	0928	0928	B31: 2.33	B62: 10.35
B32, B63	1.0	"	0943	0943	B32: 2.66	B63: 10.21
B33, B64	1.33	"	1003	1003	B33: 3.28	B64: 9.75
B34, B65	1.66	"	1023	1023	B34: 3.56	B65: 9.35
B35, B66	2.0	"	1043	1043	B35: 4.57	B66: 8.88
B36	2.5	"	1113	1113	B36: 4.54	
B37, B67	3.0	"	1143	1143	B37: 4.2	B67: 8.49
B38	3.5	"	1213	1213	B38: 6.62	
B39, B68	4.0	"	1243	1243	B39: 5.67	B68: 8.83
B40	5.0	"	1343	1343	B40: 5.76	
B41, B69	6.0	"	1443	1443	B41: 2.01	B69: 10.08
B42	7.0	"	1543	1543	B42: 2.21	
B43	8.0	"	1643	1643	B43: *	B69A: 10.68
B44	10.0	"	1843	1843	B44: *	10.86

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	07 JAN 86	0843	0843	PO	N/A

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H M F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	07 JAN 86	0843	0843	PO	W/A

DOSAGE (total)

16 mg.

PHYSIOLOGIC VARIABLES

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	07 JAN 86	0808	0808	#76	#51/55	#OK
	0.25	"	0858	0858	#74		
	0.50	"	0915	0915	#68	#55/48	#OK
	0.75	"	0928	0928	#78		
	1.0	"	0943	0943	#64	#51/48	
	1.33	"	1003	1003	#80		
	1.66	"	1023	1023	#60		
	2.00	"	1043	1043	#64	#57/58	
	2.5						
	3.0	"	1143	1143	#62		
	3.5						
	4.0	"	1243	1243	#72	#54/54	
	5.0						
	6.0	"	1443	1443	#72	#53/54	
	7.0						
	8.0						
	10.0						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>H</u> <u>M</u> F M L	010	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	07 JAN 86	0843	0843	PO	N/A

DOSAGE (total) 16 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> <u>F M L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	02 JAN 86 ddmmmyy	06 JAN 86 ddmmmyy	07 JAN 86 ddmmmyy	07 JAN 86 ddmmmyy	08 JAN 86 ddmmmyy	Date
NA: 135-148 MEQ/L	142	138	136		138	
K: 3.5-5.0 MEQ/L	4.7	4.5	5.0		5.1	
CL: 96-109 MEQ/L	104	104	99		104	
CO2: 24-30 MEQ/L	30	29	23		25	
SUN: 12-25 MG/DL	10	14	9		14	
CREAT: 0.4-1.5 MG/DL	1.0	1.0	1.0		1.1	
GLU: 70-115 MG/DL	78	71	75		81	
T. BILI: 0.3-1.2 MG/DL	0.8	0.3	0.7		0.6	
D. BILI: 0.1-0.4 MG/DL	0.1	0.0	0.1		0.1	
CA: 9.0-11.0 MG/DL	10.0	10.0	9.8		10.4	
PO4: 3.0-4.5 MG/DL	3.6	3.0	3.8		4.1	
URIC A: 4.2-8.8 MG/DL	5.6	5.5	5.5		5.5	
T. PROT: 6.0-8.5 G/DL	7.6	7.3	7.4		ND	
ALB.: 3.2-5.3 G/DL	5.1	4.9	4.8		5.1	
AST: 0-35 IU/L	29	20	24		22	
ALT: 0-30 IU/L	35	28	27		27	
ALK PHOS: 0-95 IU/L	40	36	33		39	
CHOL: 151-268 MG/DL	ND	ND	211		236	
LDH: 0-200 IU/L	ND	137	173	139	150	
CPK: 0-160 U/L (male)	ND	147	122	110	94	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> F M L	<u>810</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NA</u> ddmmmyy	<u>NA</u> ddmmmyy	<u>10 JAN 86</u> ddmmmyy	<u>11 JAN 86</u> ddmmmyy	Date
NA: 135-148 MEQ/L	<u>?</u>	<u> </u>		<u>139</u>	
K: 3.5-5.0 MEQ/L				<u>4.5</u>	
CL: 96-109 MEQ/L				<u>105</u>	
CO2: 24-30 MEQ/L				<u>25</u>	
SUN: 12-25 MG/DL				<u>20</u>	
CREAT: 0.4-1.5 MG/DL				<u>0.9</u>	
GLU: 70-115 MG/DL				<u>77</u>	
T. BILI: 0.3-1.2 MG/DL				<u>0.5</u>	
D. BILI: 0.1-0.4 MG/DL				<u>0.0</u>	
CA: 9.0-11.0 MG/DL				<u>9.6</u>	
PO4: 3.0-4.5 MG/DL				<u>4.1</u>	
URIC A: 4.2-8.8 MG/DL				<u>4.9</u>	
T. PROT: 6.0-8.5 G/DL				<u>7.5</u>	
ALB.: 3.2-5.3 G/DL				<u>4.8</u>	
AST: 0-35 IU/L				<u>44</u>	
ALT: 0-30 IU/L				<u>31</u>	
ALK PHOS: 0-95 IU/L				<u>35</u>	
CHOL: 151-268 MG/DL				<u>220</u>	
LDH: 0-200 IU/L				<u>171</u>	
CPK: 0-160 U/L (male)				<u>2060</u>	<u>2020</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>14</u> <u>M</u> <u>F</u> <u>M</u> <u>L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

		Screen	Predrug	Study		
		Date				
TEST	NORMAL	02 JAN 86 ddmmmyy	06 JAN 86 ddmmmyy	07 JAN 86 ddmmmyy	08 JAN 86 ddmmmyy	11 JAN 86 ddmmmyy
Hgb	13.9-16.3	15.2	14.2	14.6	15.1	13.4
PCV	41.0-53.0	44.5	40.5	43.5	45.5	39.9
Plt	150-350	224	215	208	241	261
RBC	4.50-5.90	5.49	4.88	5.35	5.54	4.89
WBC	4500-11000	4900	6700	6300	6100	7700
Bands	2-6%	1	5	9	4	16
Polys	31-76%	60	66	47	60	46
Eos	1-4%	0	0	4	0	1
Bas		0	1	0	0	2
Lymphs	24-44%	30	21	27	25	25
Atyp Lym		0	1	0	0	0
Monos	2-11%	9	6	13	11	10
Other		0	0	0	0	0
Retics	0.5-1.5%	ND	ND	1.0	0.8	1.2

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> F M L	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*Johns Hopkins University
Clinical Pharmacology*

Screen Predrug

Study

TEST	NORMAL	02 JAN 86 ddmmmyy	06 JAN 86 ddmmmyy	08 JAN 86 ddmmmyy	10 JAN 86 ddmmmyy	_____ Date ddmmmyy
Color/Sp		yellow	yellow	clear	clear	
Gr.		1.023	1.017	1.018	1.019	
pH		6.5	6.0	6.0	5.0	
Protein		neg	neg	neg	trace	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		rare	0	0	0	
Casts		0	0	0	0	
Epi. Cel		0	0	0	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
02 JAN 86	✓		
06 JAN 86	✓		
11 JAN 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H M</u> <u>F M L</u>	<u>010</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred ☐

ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)	
#						
1	Hot and cold flashes, inital	10 Jan 86 dd mmm yy	10 Jan 86 dd mmm yy	<input checked="" type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input checked="" type="checkbox"/> None
	1430 (0-2400)	1500 (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment	
			<input type="checkbox"/> Sev	<input checked="" type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug	
				<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> Stop test drug	
				<input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug	
#						
	dd mmm yy	dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None	
			<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment	
	(0-2400)	(0-2400)	<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug	
				<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> Stop test drug	
				<input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>L</u> <u>H</u> <u>F</u> <u>M</u> <u>L</u>	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmmyy	Procedures
—	02 JAN 86	Screening laboratory
—	09 JAN 86	History, Physical Exam
0	12 JAN 86	Admission
2	13 JAN 86	I.V.
5	16 JAN 86	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 011.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent Pittley M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R L H</u> <u>F M L</u>	<u>011</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 09, JAN, 86
dd mm yy

Examiner

Brent G. Petty MD

Date of birth 13, Aug, 57
dd mm yy

Brent G. Petty
print name

Age 28-yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	<u>1/2 - 1 ppd</u>
Alcohol Use		✓	<u>2 cans/day on weekends</u>
Recreational Drug Use		✓	<u>Marijuana 93 wks</u>
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	<u>Pharmaceuticals 2 yrs ago</u>
Blood or plasma donor		✓	<u>Last Oct 1985</u>
Prior Surgery		✓	<u>Append 1978, tonsillectomy 1975</u>
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	<u>Syphilis 1977</u> <u>G.C. 1979 - Rx PCN</u>
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 09 JAN 86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4</u> C	<u>80</u> /min	<u>16</u> /min	<u>110/20</u>	<u>179.0</u>	<u>77.1</u>

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	/		
EENT	/		Residual tonsillar tissue on R
Chest, lungs	/		
Heart	/		
Abdomen	/		
Genitalia			N.D.
Rectal			N.D.
Extremities	/		
Skin	/		
Neurologic	/		

CHEST X-RAY

Date 09 JAN 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD

Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1015	1045	IV	NA

Syringe + pyrido = 42.35694 g
 Syringe - pyrido = 22.34901 g

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	13 JAN 86	N.A.	08:14 08:26	B01: *	B47: 15.08
B02	0.08	"	1020	1020	B02: 5.11	
B03	0.16	"	1025	1025	B03: N.R.	
B04, B48	0.25	"	1030	1030	B04: 3.37	B48: 13.19
B05	0.33	"	1035	1035	B05: 19.2	
B06	0.42	"	1040	1040	B06: 23.3	
B07, B49	0.50	"	1045	1045	B07: 27.8	B49: 10.76
B08	0.58	"	1050	1050	B08: 25.7	
B09	0.66	"	1055	1055	B09: 19.5	
B10, B50	0.75	"	1100	1100	B10: 13.9	B50: 10.79
B11	0.83	"	1105	1105	B11: 12.7	
B12	0.92	"	1110	1110	B12: 9.38	
B13, B51	1.0	"	1115	1115	B13: 8.65	B51: 11.36
B14, B52	1.33	"	1135	1135	B14: 6.10	B52: 11.85
B15, B53	1.66	"	1155	1155	B15: 6.07	B53: 12.99
B16, B54	2.0	"	1215	1215	B16: 4.07	B54: 12.99
B17	2.5	"	1245	1245	B17: 3.31	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	Pyridostigmine
			PROTOCOL
			DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1015	1045	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	13 JAN 86	1315	1315	B18: 3.86	B55: 14.12
B19	3.5	"	1345	1345	B19: 3.23	
B20, B56	4.0	"	1415	1415	B20: 2.70	B56: 14.75
B21	5.0	"	1515	1515	B21: 2.01	
B22, B57	6.0	"	1615	1615	B22: *	B57: 14.76
B23	7.0	"	1715	1715	B23: *	
B24	8.0	"	1815	1815	B24: *	
B25	10.0	"	2015	2015	B25: *	
B26	12.0	"	2215	2215	B26: *	
B27, B58	24.0	"	1015	1015	B27: *	B58: 15.48

* below assay sensitivity 295

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1015	1045	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

NB: Mechanical hand grip meter used. Believed to be accurate.

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	13 JAN 86	N.A.	0826	#64	#43/55	#ok
	0.8	"	1020	1020			
	0.16	"	1025	1025			
	0.25	"	1030	1030	#68		
	0.33	"	1035	1035			
	0.42	"	1040	1040			
	0.50	"	1045	1045	#70	#43/56	#ok
	0.58	"	1050	1050			
	0.66	"	1055	1055			
	0.75	"	1100	1100	#68		
	0.83	"	1105	1105			
	0.92	"	1110	1110			
	1.0	"	1115	1115	#68	#43/50	
	1.33	"	1135	1135	#70		
	1.66	"	1155	1155	#66		
	2.0	"	1215	1215	#70	#39/52	
	2.5	"	1245	1245			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>2</u> <u>H</u> F M L	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1015	1045	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	13 JAN 86	1315	1315	#70		
	3.5	"	1345	1345			
	4.0	"	1415	1415	#64	#44/48	
	5.0	"	1515	1515			
	6.0	"	1615	1615	#68	#48/48	
	7.0	"	1715	1715			
	8.0	"	1815	1815			
	10.0	"	2015	2015			
	12.0	"	2215	2215			
	24.0	14 JAN 86	1015	1015	#60	#54/44	#ok

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0820	0820	PO	NA

Syringe 2 pyridos = 7.61223 g DOSAGE (total) 16 mg.
 Syringe 5 pyridos = 5.94095

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	16 JAN 86	N.A.	0804	B28: *	B59: 14.81
B29, B60	0.25	"	0835	0835	B29: 5.11	B60: 14.99
B30, B61	0.50	"	0850	0850	B30: 12.7	B61: 12.99
B31, B62	0.75	"	0905	0905	B31: 17.2	B62: 11.51
B32, B63	1.0	"	0920	0920	B32: 19.3	B63: 10.29
B33, B64	1.33	"	0940	0940	B33: 23.7	B64: 9.76
B34, B65	1.66	"	1000	1000	B34: 19.9	B65: 9.74
B35, B66	2.0	"	1020	1020	B35: 16.3	B66: 10.55
B36	2.5	"	1050	1050	B36: 14.6	
B37, B67	3.0	"	1120	1120	B37: 14.8	B67: 10.58
B38	3.5	"	1150	1150	B38: 9.84	
B39, B68	4.0	"	1220	1220	B39: 11.9	B68: 11.17
B40	5.0	"	1320	1320	B40: 9.18	
B41, B69	6.0	"	1420	1420	B41: 7.99	B69: 12.24
B42	7.0	"	1520	1520	B42: 6.88	
B43	8.0	"	1620	1620	B43: 5.08	B69A: 13.39
B44	10.0	"	1820	1820	B44: 2.04	14.07

* Dubau assay sensitivity 298

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0820	0820	PO	NA

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	R L H F M L	OT	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0820	0820	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	16 JAN 86	NA	0810	#84	# ND	# ok
	0.25	"	0835	0839	#78		-
	0.50	"	0850	0850	#80	# ND	# ok
	0.75	"	0905	0905	#78		
	1.0	"	0920	0920	#72	# ND	
	1.33	"	0940	0940	#76		
	1.66	"	1000	1000	#80		
	2.00	"	1020	1020	#64	# ND	
	2.5	"	1050	1050			
	3.0	"	1120	1120	#64		
	3.5	"	1150	1150			
	4.0	"	1220	1220	#84	# ND	
	5.0	"	1320	1320			
	6.0	"	1420	1420	#88	# ND	
	7.0	"	1520	1520			
	8.0	"	1620	1620			
	10.0	"	1820	1820			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	02 JAN 86 ddmmmyy	12 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	16 JAN 86 ddmmmyy	Date
NA: 135-148 MEQ/L	143	141	143	141		
K: 3.5-5.0 MEQ/L	4.3	4.4	4.2	4.1		
CL: 96-109 MEQ/L	109	107	107	104		
CO2: 24-30 MEQ/L	23	24	19	26		
SUN: 12-25 MG/DL	12	13	12	15		
CREAT: 0.4-1.5 MG/DL	1.1	1.3	1.2	1.4		
GLU: 70-115 MG/DL	74	103	63	65		
T. BILI: 0.3-1.2 MG/DL	0.8	0.4	0.7	ND		
D. BILI: 0.1-0.4 MG/DL	0.1	0.0	0.1	0.1		
CA: 9.0-11.0 MG/DL	9.3	8.9	9.6	9.9		
PO4: 3.0-4.5 MG/DL	4.0	4.3	3.9	3.8		
URIC A: 4.2-8.8 MG/DL	4.7	4.9	5.1	5.3		
T. PROT: 6.0-8.5 G/DL	6.4	6.1	6.6	6.8		
ALB.: 3.2-5.3 G/DL	4.2	3.8	4.1	4.3		
AST: 0-35 IU/L	31	34	24	32		
ALT: 0-30 IU/L	23	25	25	27		
ALK PHOS: 0-95 IU/L	45	41	52	46		
CHOL: 151-268 MG/DL	ND	160	189	188		
LDH: 0-200 IU/L	ND	126	ND	129	136	
CPK: 0-160 U/L (male)	NP	644	401	359	339	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R L H</u> <u>F M L</u>	<u>011</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory Johns Hopkins Hospital

	N.A. Screen	N.A. Predrug	Study	Date
TEST: NORMAL	<u>17 JAN 86</u> ddmmmyy	<u>17 JAN 86</u> ddmmmyy	<u>17 JAN 86</u> ddmmmyy	<u>17 JAN 86</u> ddmmmyy
NA: 135-148 MEQ/L			144	
K: 3.5-5.0 MEQ/L			4.4	
CL: 96-109 MEQ/L			106	
CO2: 24-30 MEQ/L			26	
SUN: 12-25 MG/DL			ND	
CREAT: 0.4-1.5 MG/DL			1.2	
GLU: 70-115 MG/DL			78	
T. BILI: 0.3-1.2 MG/DL			0.9	
D. BILI: 0.1-0.4 MG/DL			0.1	
CA: 9.0-11.0 MG/DL			9.8	
PO4: 3.0-4.5 MG/DL			4.1	
URIC A: 4.2-8.8 MG/DL			5.3	
T. PROT: 6.0-8.5 G/DL			7.1	
ALB.: 3.2-5.3 G/DL			4.4	
AST: 0-35 IU/L			32	
ALT: 0-30 IU/L			22	
ALK PHOS: 0-95 IU/L			46	
CHOL: 151-268 MG/DL			180	
LDH: 0-200 IU/L			132	
CPK: 0-160 U/L (male)			320	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen	Predrug	Study		
		02 JAN 86	12 JAN 86	14 JAN 86	17 JAN 86	Date
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Hgb	13.9-16.3	14.7	14.5	15.8	ND	
PCV	41.0-53.0	41.8	42.7	46.7	ND	
Plt	150-350	243	254	265	ND	
RBC	4.50-5.90	4.34	4.47	4.88	ND	
WBC	4500-11000	7900	7900	7300	ND	
Bands	2-6%	5	8	4	ND	
Polys	31-76%	42	42	40	ND	
Eos	1-4%	0	0	0	ND	
Bas		1	0	1	ND	
Lymphs	24-44%	44	46	37	ND	
Atyp Lym		2	0	11	ND	
Monos	2-11%	6	4	7	ND	
Other		0	0	0	ND	
Retics	0.5-1.5%	ND	0.8	N.D.	ND	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{R}{F} \frac{L}{M} \frac{H}{L}$	011	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

University
Johns Hopkins Hospital
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	09 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	17 JAN 86 ddmmmyy	----- ddmmmyy	Date
Color/Sp		yellow	yellow	yellow	milky		
Sp. Gr.		1.019	1.019	1.023	1.019		
pH		7.0	6.0	7.5	7.0		
Protein		trace	trace	2+	trace		
Ketones		neg	neg	neg	neg		
Occ Bld		neg	neg	neg	neg		
Bili.		neg	neg	neg	neg		
RBC		0	0	0	0		
WBC		0	0	0	0		
Casts		0	0	0	0		
Epi. Cel		0	0	0	0		
Crystals		0	0	0	0		
Bacteria		0	0	0	0		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
09 JAN 86	✓		
14 JAN 86	✓		
17 JAN 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R L H</u> F M L	011	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
				<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
		(0-2400)	(0-2400)	<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> UNKNOWN
#		dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
				<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
		(0-2400)	(0-2400)	<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> UNKNOWN

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> F <u>W</u> M <u>B</u> L	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	06 JAN 86	Screening laboratory
—	09 JAN 86	History, Physical Exam
0	12 JAN 86	Admission
2	13 JAN 86	IV
5	16 JAN 86	PO

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 012.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Bruce G. Petty M.D.
Investigator's signature

24 JAN 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A W B</u> F M L	<u>012</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 09 JAN 86
dd mm yy

Examiner Brent G. Petty MD

Date of birth 27 JUN 56
dd mm yy

Brent G. Petty
print name

Age 29 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	1/2 ppd
Alcohol Use		✓	1 pt gin 1 wk. 2 6 packs/wk end
Recreational Drug Use		✓	Occ. marijuana - last ~ 3 days ago, average ~ 3/wk
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Tobramycin - here Pharm. - kinetics
Blood or plasma donor		✓	Last ~ 4 months ago
Prior Surgery		✓	Broke foot, had some bone removed 1984
Eye, ear, nose, throat		✓	glasses x 8 yrs.
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Last just before Christmas and then 2 days ago.
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A W B</u> F M L	<u>012</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 09/ JAN/ 86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4 C</u>	<u>68/min</u>	<u>20/min</u>	<u>120/64</u>	<u>182.0</u>	<u>79.2</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			N.D.
Rectal			N.D.
Extremities	✓		
Skin		✓	scars both wrists, (R) upper arm, (L) forearm small tattoo (R) forearm
Neurologic	✓		

CHEST X-RAY

Date 09/ JAN/ 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL	<input type="checkbox"/>	Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{W}{M} \frac{B}{L}$	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1018	1048	IV	NA

syringe + pyrids = 42.55140g
 syringe - pyrids = 22.48629g

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	REC ACHe uM/ml/min
B01, B47	0	13 JAN 86	NA	0810	B01: *	B47: 15.28
B02	0.08	"	1023	1023	B02: 3.37	
B03	0.16	"	1028	1028	B03: 10.4	
B04, B48	0.25	"	1033	1033	B04: 20.3	B48: 12.27
B05	0.33	"	1038	1038	B05: 30.9	
B06	0.42	"	1043	1043	B06: 28.1	
B07, B49	0.50	"	1048	1048	B07: 22.1	B49: 10.27
B08	0.58	"	1053	1053	B08: 16.3	
B09	0.66	"	1058	1058	B09: 12.8	
B10, B50	0.75	"	1103	1103	B10: 17.3	B50: 10.84
B11	0.83	"	1108	1108	B11: 8.30	
B12	0.92	"	1113	1113	B12: 8.36	
B13, B51	1.0	"	1118	1118	B13: 9.06	B51: 11.55
B14, B52	1.33	"	1138	1138	B14: 6.17	B52: 11.68
B15, B53	1.66	"	1158	1158	B15: 4.66	B53: 13.61
B16, B54	2.0	"	1218	1218	B16: 3.31	B54: 13.37
B17	2.5	"	1248	1248	B17: 2.58	

* below assay sensitivity 310

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>W</u> <u>B</u> F M L	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1018	1048	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 311

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>F</u> <u>w</u> <u>M</u> <u>B</u> <u>L</u>	<u>D12</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1018	1048	IV	NA

DOSAGE (total) 1.32mg.**PHYSIOLOGIC VARIABLES**

NB: Mechanical hand grip used. Believed to be

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	13 JAN 86	NA	0827	#52	#46/45	#ok
	0.8	"	1023	1027			
	0.16	"	1028	1028			
	0.25	"	1033	1033	#60		
	0.33	"	1038	1038			
	0.42	"	1043	1043			
	0.50	"	1048	1048	#64	#53/56	#ok
	0.58	"	1053	1053			
	0.66	"	1058	1058			
	0.75	"	1103	1103	#64		
	0.83	"	1108	1108			
	0.92	"	1113	1113			
	1.0	"	1118	1118	#64	#49/58	
	1.33	"	1138	1138	#60		
	1.66	"	1158	1158	#52		
	2.0	"	1218	1218	#60	#51/53	
	2.5	"	1248	1248			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A W B</u> <u>F M L</u>	<u>012</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	13 JAN 86	1018	1048	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	13 JAN 86	1318	1318	#76		
	3.5	"	1348	1348			
	4.0	"	1418	1418	#60	#48/56	
	5.0	"	1518	1518			
	6.0	"	1618	1618	#72	#45/48	
	7.0	"	1718	1718			
	8.0	"	1818	1818			
	10.0	"	2018	2018			
	12.0	"	2218	2218			
	24.0	14 JAN 86	1018	1018	#ND	#ND	#ND

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>W</u> <u>B</u> <u>F</u> <u>M</u> <u>L</u>	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0823	0823	PO	N.A.

Syringe 2 pyrido = 7.65615g
 Syringe 5 pyrido = 5.97785g

DOSAGE (total)

16 mg.**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	16 JAN 86	NA	0815	B28: *	B59: 14.98
B29, B60	0.25	"	0838	0838	B29: *	B60: 15.25
B30, B61	0.50	"	0853	0853	B30: 5.67	B61: 13.96
B31, B62	0.75	"	0908	0908	B31: 4.49	B62: 13.38
B32, B63	1.0	"	0923	0923	B32: 6.28	B63: 12.86
B33, B64	1.33	"	0943	0943	B33: 7.04	B64: 12.23
B34, B65	1.66	"	1003	1003	B34: 11.7	B65: 11.53
B35, B66	2.0	"	1023	1023	B35: 13.9	B66: 10.94
B36	2.5	"	1053	1053	B36: 13.2	
B37, B67	3.0	"	1123	1123	B37: 8.75	B67: 10.56
B38	3.5	"	1153	1153	B38: 12.2	
B39, B68	4.0	"	1223	1223	B39: 10.2	B68: 11.28
B40	5.0	"	1323	1323	B40: 6.62	
B41, B69	6.0	"	1423	1423	B41: 4.10	B69: 13.37
B42	7.0	"	1523	1523	B42: 2.70	
B43	8.0	"	1623	1623	B43: 250	B69A: 13.96
B44	10.0	"	1823	1823	B44: *	14.74

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{A}{F} \frac{W}{M} \frac{B}{L}$	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0823	0823	PO	N/A

DOSAGE (total)

16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	16 JAN 86	N.A.	0815	# 64	# ND	# ND
	0.25	"	0828	0839	# 64		-
	0.50	"	0853	0853	# 70	# ND	# ok
	0.75	"	0908	0908	# 72		
	1.0	"	0923	0923	# 64	# ND	
	1.33	"	0943	0943	# 68		
	1.66	"	1003	1003	# 70		
	2.00	"	1023	1023	# 60	# ND	
	2.5	"	1053	1053			
	3.0	"	1123	1123	# 64		
	3.5	"	1153	1153			
	4.0	"	1223	1223	# 84	# ND	
	5.0	"	1323	1323			
	6.0	"	1423	1423	# 84	# ND	
	7.0	"	1523	1523			
	8.0	"	1623	1623			
	10.0	"	1823	1823			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>F</u> <u>M</u> <u>L</u>	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	16 JAN 86	0823	0823	PO	N/A

DOSAGE (total) 16 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	<u>A W B</u> <u>F M L</u>	012	PROTOCOL	DAMD 17-85-C-5133-02

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	06 JAN 86 ddmmmyy	12 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	16 JAN 86 ddmmmyy
NA: 135-148 MEQ/L	138	140		140	
K: 3.5-5.0 MEQ/L	4.0	4.3		4.1	
CL: 96-109 MEQ/L	106	106		108	
CO2: 24-30 MEQ/L	27	26		24	
SUN: 12-25 MG/DL	8	12		9	
CREAT: 0.4-1.5 MG/DL	1.0	1.1		1.2	
GLU: 70-115 MG/DL	90	100		84	
T. BILI: 0.3-1.2 MG/DL	0.3	N.D.		N.D.	
D. BILI: 0.1-0.4 MG/DL	0.1	0.0		0.0	
CA: 9.0-11.0 MG/DL	9.1	8.9		9.4	
PO4: 3.0-4.5 MG/DL	2.8	3.4		2.4	
URIC A: 4.2-8.8 MG/DL	5.3	6.7		6.5	
T. PROT: 6.0-8.5 G/DL	6.1	6.2		6.0	
ALB.: 3.2-5.3 G/DL	3.9	3.9		4.0	
AST: 0-35 IU/L	13	19		18	
ALT: 0-30 IU/L	14	9		13	
ALK PHOS: 0-95 IU/L	44	38		43	
CHOL: 151-268 MG/DL	ND	127 123		153	
LDH: 0-200 IU/L	ND	123	132	110	122
CPK: 0-160 U/L (male)	ND	181	94	79	78

NB - no follow up labs on 17 Jan 86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A W S</u> <u>F M L</u>	<u>012</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUESLaboratory Johns Hopkins Hospital

		Screen	Predrug	Pre drug	Study	
TEST	NORMAL	<u>06 JAN 86</u> ddmmmyy	<u>12 JAN 86</u> ddmmmyy	<u>13 JAN 86</u> ddmmmyy	<u>14 JAN 86</u> ddmmmyy	<u>17 JAN 86</u> ddmmmyy
Hgb	13.9-16.3	14.1	14.7	14.1	15.1	N.D.
PCV	41.0-53.0	41.5	42.9	46.0	44.3	N.D.
Plt	150-350	225	184	154	215	N.D.
RBC	4.50-5.90	4.17	4.34	4.54	4.42	N.D.
WBC	4500-11000	5700	5300	4400	6600	N.D.
Bands	2-6%	1	10	0	4	N.D.
Polys	31-76%	72	59	59	58	N.D.
Eos	1-4%	2	3	6	2	N.D.
Bas		0	0	0	1	N.D.
Lymphs	24-44%	18	24	30	26	N.D.
Atyp Lym		0	0	0	1	N.D.
Monos	2-11%	7	4	5	8	N.D.
Other		0	0	0	0	N.D.
Retics	0.5-1.5%	N.D.	1.0	N.D.	N.D.	N.D.

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A</u> <u>W</u> <u>B</u> F M L	012	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

		Screen		Predrug		Study	
TEST	NORMAL	N.D.		13 JAN 86	14 JAN 86	17 JAN 86	Date
		ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Color/Sp				yellow	clear	clear	
Sp. Gr.				1.023	1.019	1.024	
pH				6.0	6.0	7.0	
Protein				neg	trace	neg	
Ketones				neg	neg	neg	
Occ Bld				neg	neg	neg	
Bili.				neg	neg	neg	
RBC				0	0	0	
WBC				0	0	0	
Casts				0	0	0	
Epi. Cel				0	0	0	
Crystals				0	0	0	
Bacteria				0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
09 JAN 86	✓		
14 JAN 86	✓		
17 JAN 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>A W B</u> F M L	<u>012</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>F</u> <u>R</u> <u>F</u> <u>M</u> <u>L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	07JAN86	Screening laboratory
—	09JAN86	History, Physical Exam
0	13JAN86	Admission
2	14JAN86	PO
5	17JAN86	IV

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # B.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	<u>013</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 09 JAN 86
dd mm yy

Examiner Brent G. Petty

Date of birth 27 SEP 55
dd mm yy

Brent G. Petty
print name

Age 30 yrs

Sex M

Race C

	No	Yes	Comments
Allergy	✓		
Tobacco Use	✓		
Alcohol Use		✓	Six packs/week, one cocktail
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Interferon, ceftriaxone.
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Insecticide last year (summer 1985)
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>E</u> <u>R</u> <u>F</u> <u>M</u> <u>L</u>	<u>013</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/09/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.5</u> C	<u>68</u> /min	<u>20</u> /min	<u>112/78</u>	<u>173.0</u>	<u>62.7</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	<u>Sclerotic @ TM, @ CHC drumming</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		<u>ND</u>	
Rectal		<u>ND</u>	
Extremities	✓		
Skin		✓	<u>Scars @ index finger + @ dorsal hand area</u>
Neurologic	✓		

CHEST X-RAY

Date 10/JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner Brent G. Petty MD

Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	W F R F M L	013	Pyridostigmine DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0827	0857	IV	NA

Syringe + pyrido = 41.77491

Syringe - pyrido = 21.83540 DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	17 JAN 86	0815	0815	B01: *	B47: 13.41
B02	0.08	"	0832	0832	B02: 8.78	
B03	0.16	"	0837	0837	B03: 11.7	
B04, B48	0.25	"	0842	0842	B04: 25.0	B48: 10.90
B05	0.33	"	0847	0847	B05: 32.5	
B06	0.42	"	0852	0852	B06: 19.7	
B07, B49	0.50	"	0857	0857	B07: 46.8	B49: 8.16
B08	0.58	"	0902	0902	B08: 15.2	
B09	0.66	"	0907	0907	B09: 14.1	
B10, B50	0.75	"	0912	0912	B10: 11.2	B50: 10.17
B11	0.83	"	0917	0917	B11: 8.34	
B12	0.92	"	0922	0922	B12: 6.12	
B13, B51	1.0	"	0927	0927	B13: 7.06	B51: 10.75
B14, B52	1.33	"	0947	0947	B14: 2.50	B52: 11.60
B15, B53	1.66	"	1007	1007	B15: 2.34	B53: 12.18
B16, B54	2.0	"	1027	1027	B16: *	B54: 12.67
B17	2.5	"	1057	1057	B17: *	

* below assay sensitivity 2.25

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0827	0857	IV	W/A

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{W}{F} \frac{F}{M} \frac{R}{L}$	013	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0827	0857	IV	NA

DOSAGE (total)

1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	17 JAN 86	NA	Not Recorded	#68	#N.D.	#ok
	0.8	"	0832	0832			
	0.16	"	0837	0837			
	0.25	"	0842	0842	#70		
	0.33	"	0847	0847			
	0.42	"	0852	0852			
	0.50	"	0857	0857	#78	#ND	#ok
	0.58	"	0902	0902			
	0.66	"	0907	0907			
	0.75	"	0912	0912	#70		
	0.83	"	0917	0917			
	0.92	"	0922	0922			
	1.0	"	0927	0927	#64	#ND	
	1.33	"	0947	0947	#74	ND	
	1.66	"	1007	1007	#ND		
	2.0	"	1027	1027	#60	#ND	
	2.5	"	1057	1057			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{W}{F} \frac{F}{M} \frac{R}{L}$	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 Jan 86	0827	0857	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{W}{F} \frac{F}{M} \frac{R}{L}$	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14JAN86	0853	0853	PO	NA

syringe + pyrid = 7.65328g
 syringe - syringe = 5.97348g

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	14JAN86	0822	0822	B28: *	B59: 13.15
B29, B60	0.25	"	0908	0908	B29: *	B60: 13.19
B30, B61	0.50	"	0923	0923	B30: 7.61	B61: 11.55
B31, B62	0.75	"	0938	0938	B31: 13.5	B62: 10.47
B32, B63	1.0	"	0953	0953	B32: 12.8	B63: 9.52
B33, B64	1.33	"	1013	1013	B33: 16.8	B64: 8.86
B34, B65	1.66	"	1033	1033	B34: 14.4	B65: 8.80
B35, B66	2.0	"	1053	1053	B35: 14.3	B66: 9.00
B36	2.5	"	1123	1123	B36: 16.7	
B37, B67	3.0	"	1153	1153	B37: 13.5	B67: 8.49
B38	3.5	"	1223	1223	B38: 13.4	
B39, B68	4.0	"	1253	1253	B39: 11.1	B68: 8.64
B40	5.0	"	1353	1353	B40: 16.2	
B41, B69	6.0	"	1423 1453	1453	B41: 5.55	B69: 10.72
B42	7.0	"	1553 1653	1553	B42: 3.17	
B43	8.0	"	1653	1653	B43: 4.21	B69A: 11.47
B44	10.0	"	1853	1853	B44: *	12.15

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14 JAN 86	0853	0853	PO	NA

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 330

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14 JAN 86	0853	0853	PO	NA

DOSAGE (total) 16mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	14 JAN 86	0851	0851	#60	#ND	#ok
	0.25	"	0908	0908	#72		-
	0.50	"	0923	0923	#70	#ND	#ok
	0.75	"	0938	0933	#80		
	1.0	"	0953	0953	#78	#ND	
	1.33	"	1013	1013	#60		
	1.66	"	1033	1033	#60		
	2.00	"	1053	1053	#62	#ND	
	2.5	"	1123	1123			
	3.0	"	1153	1153	#60		
	3.5	"	1223	1223			
	4.0	"	1253	1253	#64	#ND	
	5.0	"	1353	1353			
	6.0	"	1453	1453	#68	#ND	
	7.0	"	1553	1553 1653			
	8.0	"	1653	1653			
	10.0	"	1853	1853			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W</u> <u>F</u> <u>R</u> <u>F</u> <u>M</u> <u>L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14 JAN 86	0853	0853	PO	NA

DOSAGE (total) 16 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{W}{F} \frac{F}{M} \frac{I}{L}$	013	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST:NORMAL	07 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	15 JAN 86 ddmmmyy	18 JAN 86 ddmmmyy
NA:135-148 MEQ/L	143	140		144	141
K:3.5-5.0 MEQ/L	5.0	4.1		4.9	4.0
CL:96-109 MEQ/L	105	104		105	107
CO2:24-30 MEQ/L	25	28		24	24
SUN:12-25 MG/DL	16	14		16	14 12
CREAT:0.4-1.5 MG/DL	1.0	1.0		1.0	1.0 0.9
GLU:70-115 MG/DL	87	89		91	76
T. BILI:0.3-1.2 MG/DL	0.3	0.4		0.3	0.3
D. BILI:0.1-0.4 MG/DL	0.0	0.0		0.0	0.0
CA:9.0-11.0 MG/DL	10.1	ND		10.4	9.6
PO4:3.0-4.5 MG/DL	4.2	5.3		4.1	3.5
URIC A:4.2-8.8 MG/DL	5.1	4.9		5.9	5.3
T. PROT:6.0-8.5 G/DL	7.4	7.1		7.8	7.4
ALB.:3.2-5.3 G/DL	4.7	4.5		4.8	4.5
AST:0-35 IU/L	22	35		35	33
ALT:0-30 IU/L	26	40		44	45
ALK PHOS:0-95 IU/L	69	72		71	70
CHOL:151-268 MG/DL	199	212		251	214
LDH:0-200 IU/L	ND	123		139	137
CPK:0-160 U/L (male)	ND	84	62	67	68

N.B. CPK not done on 17 Jan 86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	<u>013</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen	Predrug	Pre drug			Study
TEST	NORMAL	07 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	15 JAN 86 ddmmmyy	18 JAN 86 ddmmmyy	Date
Hgb	13.9-16.3	14.8	14.9	15.0	15.7	14.2	
PCV	41.0-53.0	43.6	42.8	44.4	46.7	41.7	
Plt	150-350	340	328	336	333	323	
RBC	4.50-5.90	4.89	4.84	5.05	5.26	4.75	
WBC	4500-11000	6300	8300	6100	6400	6200	
Bands	2-6%	7	7	7	18	4	
Polys	31-76%	54	60	44	33	42	
Eos	1-4%	1	1	5	4	7	
Bas		0	0	10	1	0	
Lymphs	24-44%	28	26	34	32	38	
Atyp Lym		0	1	2	0	0	
Monos	2-11%	10	5	8	12	9	
Other		0	0	0	0	0	
Retics	0.5-1.5%	N.D.	1.0	1.6	N.D.	1.5	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> <u>F M L</u>	013	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

John Hopkin
Clinical Pharmacology

TEST	NORMAL	Screen		Predrug		Study	
		N.D.	14 JAN 86	15 JAN 86	18 JAN 86	Date	
		ddmmyy	ddmmyy	ddmmyy	ddmmyy	ddmmyy	
Color/Sp			clear	yellow	N.D.		
Sp. Gr.			1.021	1.019	1.022		
pH			5.0	6.0	6.0		
Protein			neg	trace	neg		
Ketones			neg	neg	neg		
Occ Bld			neg	neg	neg		
Bili.			neg	neg	neg		
RBC			0	0	0		
WBC			0	0	0		
Casts			0	0	0		
Epi. Cel			0	0	0		
Crystals			0	0	0		
Bacteria			0	0	0		

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
01 AUG 83	✓		
01 JAN 86	✓		
15 JAN 86	✓		
18 JAN 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W F R</u> F M L	<u>013</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J D S</u> <u>F M L</u>	<u>014</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
-	07 01 86	Screening laboratory
-	09 JAN 86	History, Physical Exam
0	13 JAN 86	Admission
2	14 JAN 86	ORAL
5	17 JAN 86	IV

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 1525 pages, for subject # 014.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J D S</u> <u>F M L</u>	<u>014</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation

09 JAN
01/09/86

Examiner

Brent G. Petty

Date of birth

05/12/61
dd mmm yyBrent G. Petty
print name

Age

24 yrs

Sex

M

Race

W

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1 pcd
Alcohol Use		✓	6-pack/day
Recreational Drug Use		✓	Marjuana 3/wk, last time had lungs ~ 1 year ago
Medications past 2 weeks		✓	Alka Seltzer yesterday for HA
Experimental Drug Exposure		✓	Sexual
Blood or plasma donor	✓		
Prior Surgery		✓	Tonsillectomy 1971
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)		✓	Cigarettes → cough; wheezing in HA
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	1 month ago sprayed for bugs + pets in for flea
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>I D S</u> <u>F M L</u>	<u>014</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/09/86
 dd mm yy
09 JAN

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>ND</u> C	<u>ND</u> /min	<u>ND</u> /min	<u>ND</u> / <u>ND</u>	<u>176</u>	<u>86.5</u>

GENERAL EXAMINATION:

(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Druse at 10' clock (eye ~ 2 disc diameters from disc) (2) Tarsal exophthalmos (nasal septum d. to right)
Chest, lungs		✓	(2) lung & some shunt
Heart	✓		
Abdomen	✓		
Genitalia		ND	
Rectal		ND	
Extremities	✓		
Skin		✓	Tattoo (upper arm)
Neurologic	✓		

CHEST X-RAY

Date 09/ JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{J}{F} \frac{D}{M} \frac{S}{L}$	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0830	0900	IV	NA

syringe + pyrido = 41.940868
 syringe - pyrido = 21.84021

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	17 JAN 86	0820	0820	B01: *	B47: 12.46
B02	0.08	"	0835	0835	B02: 11.6	
B03	0.16	"	0840	0840	B03: 17.7	
B04, B48	0.25	"	0845	0845	B04: 23.1	B48: 10.03
B05	0.33	"	0850	0850	B05: 19.0	
B06	0.42	"	0855	0855	B06: 33.3	
B07, B49	0.50	"	0900	0900	B07: 24.5	B49: 8.51
B08	0.58	"	0905	0905	B08: 20.2	
B09	0.66	"	0910	0910	B09: 11.3	
B10, B50	0.75	"	0915	0915	B10: 6.59	B50: 9.37
B11	0.83	"	0920	0920	B11: 6.70	
B12	0.92	"	0925	0925	B12: 4.07	
B13, B51	1.0	"	0930	0930	B13: 4.42	B51: 10.23
B14, B52	1.33	"	0950	0950	B14: 3.04	B52: 10.77
B15, B53	1.66	"	1010	1010	B15: 2.92	B53: 11.23
B16, B54	2.0	"	1030	1030	B16: 2.04	B54: 11.68
B17	2.5	"	1100	1100	B17: 1.62	

* helix assay sensitivity 340

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	J D S F M L	014	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0830	0900	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] ug/mL	RBC AChE uM/ml/min
B18, B55	3.0	17 JAN 86	1130	1130	B18: *	B55: 11.76
B19	3.5	"	1200	1200	B19: *	
B20, B56	4.0	"	1230	1230	B20: *	B56: 12.28
B21	5.0	"	1330	1330	B21: *	
B22, B57	6.0	"	1430	1430	B22: *	B57: 12.54
B23	7.0	"	1530	1530	B23: *	
B24	8.0	"	1630	1630	B24: *	
B25	10.0	"	1830	1830	B25: *	
B26	12.0	"	2030	2030	B26: *	
B27, B58	24.0	18 JAN 86	0830	0830	B27: *	B58: 12.27

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J</u> <u>F</u> <u>D</u> <u>M</u> <u>L</u>	<u>019</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD**STUDY: IV PYRIDOSTIGMINE**

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>17 JAN 86</u>	<u>0830</u>	<u>0900</u>	<u>IV</u>	<u>ND</u>

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	<u>0</u>	<u>17 JAN 86</u>	<u>0820</u>	<u>0820</u>	<u>#78</u>	<u># ND</u>	<u># ck</u>
	<u>0.8</u>	<u>"</u>	<u>0835</u>				
	<u>0.16</u>	<u>"</u>	<u>0840</u>				
	<u>0.25</u>	<u>"</u>	<u>0845</u>		<u>#80</u>		
	<u>0.33</u>	<u>"</u>	<u>0850</u>				
	<u>0.42</u>	<u>"</u>	<u>0855</u>				
	<u>0.50</u>	<u>"</u>	<u>0900</u>	<u>0900</u>	<u>#84</u>	<u># ND</u>	<u># ck</u>
	<u>0.58</u>	<u>"</u>	<u>0905</u>				
	<u>0.66</u>	<u>"</u>	<u>0910</u>				
	<u>0.75</u>	<u>"</u>	<u>0915</u>	<u>0915</u>	<u>#92</u>		
	<u>0.83</u>	<u>"</u>	<u>0920</u>				
	<u>0.92</u>	<u>"</u>	<u>0925</u>				
	<u>1.0</u>	<u>"</u>	<u>0930</u>	<u>0930</u>	<u>#90</u>	<u># ND</u>	
	<u>1.33</u>	<u>"</u>	<u>0950</u>	<u>0950</u>	<u>#90</u>		
	<u>1.66</u>	<u>"</u>	<u>1010</u>	<u>1010</u>	<u>#88</u>		
	<u>2.0</u>	<u>"</u>	<u>1030</u>	<u>1030</u>	<u>#72</u>	<u># ND</u>	
	<u>2.5</u>	<u>"</u>	<u>1100</u>	<u>1100</u>			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J D S F M L	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	17 JAN 86	0830	0900	IV	NA

DOSAGE (total) 1.32mg.**PHYSIOLOGIC VARIABLES**

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Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	17 JAN 86	1130	1130	#80		
	3.5	"	1200	1200			
	4.0	"	1230	1230	#84	#ND	
	5.0	"	1330	1330			
	6.0	"	1430	1430	#ND	#ND	
	7.0	"	1530	1530			
	8.0	"	1630	1630			
	10.0	"	1830	1830			
	12.0	"	2030	2030			
	24.0	18 JAN 86	0830	0830	#60	#ND	#OK

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J D S</u> <u>F M L</u>	<u>014</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14 JAN 86	0855	0855	PO	NA

Synergie + pyrido = 7.60178 g
 Synergie - pyrido = 5.94663 g
 DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	14 JAN 86	0825	0825	B28:*	B59: 12.12
B29, B60	0.25	"	0910	0910	B29: 3.51	B60: 12.29
B30, B61	0.50	"	0925	0925	B30: 4.98	B61: 11.59
B31, B62	0.75	"	0940	0940	B31: 10.7	B62: 10.05
B32, B63	1.0	"	0955	0955	B32: 14.5	B63: 9.15
B33, B64	1.33	"	1015	1015	B33: 10.0	B64: 8.79
B34, B65	1.66	"	1035	1035	B34: 9.07	B65: 8.70
B35, B66	2.0	"	1055	1055	B35: 16.2	B66: 8.22
B36	2.5	"	1125	1125	B36: 20.9	
B37, B67	3.0	"	1155	1155	B37: 14.0	B67: 8.33
B38	3.5	"	1225	1225	B38: 13.9	
B39, B68	4.0	"	1255	1255	B39: 11.6	B68: 8.52
B40	5.0	"	1355	1355	B40: 12.7	
B41, B69	6.0	"	1455	1455	B41: 7.59	B69: 9.52
B42	7.0	"	1555	1555	B42: 6.45	
B43	8.0	"	1655	1655	B43: NS	B69A: 10.63
B44	10.0	"	1855	1855	B44: 19.2*	11.01

* below assay sensitivity
 NS. - no sample

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J</u> F <u>D</u> M <u>S</u> L	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14JAN86	0855	0855	PO	NA

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 345

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J D S F M L	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	14 JAN 86	0855	0855	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	14 JAN 86	N.A.	NOT Recorded	# 88	# ND	# ok
	0.25	"	0910	0910	# 76		-
	0.50	"	0925	0925	# 90	# ND	# ok
	0.75	"	0940	0940	# 76		
	1.0	"	0955	0955	# 80	# ND	
	1.33	"	1015	1015	# 76		
	1.66	"	1035	1035	# 78		
	2.00	"	1055	1055	# 80	# ND	
	2.5	"	1125	1125			
	3.0	"	1155	1155	# 80		
	3.5	"	1225				
	4.0	"	1255	1255	# 84	# ND	
	5.0	"	1355	1355			
	6.0	"	1455	1455	# 80	# ND	
	7.0	"	1555				
	8.0	"	1655				
	10.0	"	1855				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{P}{M} \frac{S}{L}$	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	07 JAN 86 ddmmmyy	13 JAN 86 ddmmmyy	14 JAN 86 ddmmmyy	15 JAN 86 ddmmmyy	18 JAN 86 ddmmmyy
NA: 135-148 MEQ/L	139	139		142	143
K: 3.5-5.0 MEQ/L	4.4	4.7		4.3	4.2
CL: 96-109 MEQ/L	104	103		109	107
CO2: 24-30 MEQ/L	29	26		18	25
SUN: 12-25 MG/DL	21	12		15	15
CREAT: 0.4-1.5 MG/DL	1.3	0.9		1.0	1.0
GLU: 70-115 MG/DL	88	95		92	79
T. BILI: 0.3-1.2 MG/DL	0.5	ND		1.0	0.5
D. BILI: 0.1-0.4 MG/DL	0.1	0.1		0.0	0.1
CA: 9.0-11.0 MG/DL	9.8	9.6		9.6	9.2
PO4: 3.0-4.5 MG/DL	4.5	3.4		4.1	3.9
URIC A: 4.2-8.8 MG/DL	7.2	6.0		5.3	ND
T. PROT: 6.0-8.5 G/DL	6.7	6.7		6.7	6.2
ALB.: 3.2-5.3 G/DL	4.7	4.6		4.6	4.5
AST: 0-35 IU/L	14	17		12	14
ALT: 0-30 IU/L	13	10		10	12
ALK PHOS: 0-95 IU/L	44	45		46	39
CHOL: 151-268 MG/DL	253	250		249	228
LDH: 0-200 IU/L	N.D.	160		148	142
CPK: 0-160 U/L (male)	N.D.	218	174	152	153

N.B. CPK not done on 17 Jan 86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J D S F M L	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

		Screen		Predrug		Study	
		07 JAN 86	13 JAN 86	15 JAN 86	18 JAN 86	Date	
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Hgb	13.9-16.3	16.4	16.7	16.8	15.7		
PCV	41.0-53.0	47.3	50.3	48.8	45.2		
Plt	150-350	283	314	332	308		
RBC	4.50-5.90	4.81	5.06	5.02	4.66		
WBC	4500-11000	7000	6000	7500	6600		
Bands	2-6%	5	2	13	4		
Polys	31-76%	54	54	40	46		
Eos	1-4%	3	1	1	7		
Bas		0	0	0	0		
Lymphs	24-44%	33	38	37	34		
Atyp Lym		0	0	3	0		
Monos	2-11%	5	5	6	9		
Other		0	0	0	0		
Retics	0.5-1.5%	N.D.	1.1	N.A.	1.3		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J D S</u> F M L	014	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES
Laboratory

*Johns Hopkins Hospital
Clinical Pharmacology*

		Screen Predrug				Study
		13 JAN 86	14 JAN 86	15 JAN 86	18 JAN 86	Date
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy
Color/Sp		yellow	yellow	yellow	N.D.	
Gr.		1.017	1.019	1.024	1.020	
pH		5.0	6.0	5.0	6.0	
Protein		neg	neg	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		0	0	0	0	
Casts		0	0	0	0	
Epi. Cel		0	0	0	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
09 JAN 86	✓		
15 JAN 86	✓		axis shifted rightward
18 JAN 86	✓		axis shifted leftward toward original

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>JDS</u> F M L	<u>014</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> F M L	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
-	08 JAN 86	Screening laboratory
-	15 JAN 86	History, Physical Exam
0	19 JAN 86	Admission
2	21 JAN 86	02 JAN 86 IV
5	24 JAN 86	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 015.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 JAN 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> <u>F M L</u>	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation

15 Jan
01/15/86

Examiner

Brent G. Petty
print name

Date of birth

14 Dec
12/14/64

Age

21
yrs

Sex

M

Race

B

No Yes Comments

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	1 pack x 3 yrs
Alcohol Use		✓	3 beers/d, occ liquor
Recreational Drug Use	✓		MT years ago
Medications past 2 weeks		✓	Tylenol ~ 2d ago for HT
Experimental Drug Exposure	✓	✓	University of MD. (diabetes study) HT
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC & PEN
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Over 500 months ago Out worn flea collar
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> <u>F M L</u>	<u>015</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/15/86
 dd mm yy
15 JAN 86

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.4</u> c	<u>72</u> min	<u>20</u> /min	<u>128/76</u>	<u>184.0</u>	<u>79.2</u>

GENERAL EXAMINATION:			Provide details of abnormalities
(check)	Nor.	Abn.	
Head/Neck		✓	<u>small lump just left of midline on occiput from neuro trauma.</u> <u>Thyroid top normal</u>
EENT		✓	<u>multifocal nerve fibers bilaterally. @ ear common.</u> <u>Septum d → @</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia	<u>MD</u>		
Rectal	<u>MD</u>		
Extremities	✓		
Skin		✓	<u>sl. hyperpigmented birthmark @ flank, few scars from scratches</u>
Neurologic	✓		<u>left handed</u>

CHEST X-RAY

Date 12/JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{J}{F} \frac{A}{M} \frac{H}{L}$	015	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 Jan 85	0912	0942	IV	NA

$\text{seizure} + \text{pyrido} = 42.46026$
 $\text{seizure} - \text{pyrido} = 22.27323$ DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/mL	RBC AChE uM/ml/min
B01, B47	0	21 Jan 85	NA	0825	B01: *	B47: 14.13
B02	0.08	"	0917	0917	B02: 8.11	
B03	0.16	"	0922	0922	B03: 13.9	
B04, B48	0.25	"	0927	0927	B04: 18.2	B48: 11.52
B05	0.33	"	0932	0932	B05: 16.4	
B06	0.42	"	0937	0937	B06: 14.0	
B07, B49	0.50	"	0942	0942	B07: 18.0	B49: 10.20
B08	0.58	"	0947	0947	B08: 12.5	
B09	0.66	"	0952	0952	B09: 8.67	
B10, B50	0.75	"	0957	0957	B10: 8.96	B50: 10.69
B11	0.83	"	1002	1002	B11: 5.37	
B12	0.92	"	1007	1007	B12: 3.86	
B13, B51	1.0	"	1012	1012	B13: 5.30	B51: 11.09
B14, B52	1.33	"	1032	1032	B14: 2.25	B52: 11.88
B15, B53	1.66	"	1052	1052	B15: 1.97	B53: 11.97
B16, B54	2.0	"	1112	1112	B16: 2.63	B54: 12.76
B17	2.5	"	1142	1142	B17: 1.83	

* below assay sensitivity 355

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	J A H F M L	05	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 Jan 86	0912	0942	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	21 Jan 86	1212	1212	B18: 2.07	B55: 13.34
B19	3.5	"	1242	1242	B19: *	
B20, B56	4.0	"	1312	1312	B20: *	B56: 13.95
B21	5.0	"	1412	1412	B21: *	
B22, B57	6.0	"	1512	1512	B22: *	B57: 14.00
B23	7.0	"	1612	1612	B23: *	
B24	8.0	"	1712	1712	B24: *	
B25	10.0	"	1912	1912	B25: *	
B26	12.0	"	2112	2112	B26: *	
B27, B58	24.0	22 Jan 86	0912	0912	B27: *	B58: 13.81

* below assay sensitivity 356

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J A H F M L	25	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 Jan 86	0912	0942	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	21 JAN 86	N.A.	0825	#50	#ND	#ok
	0.8	"	0917	0917			
	0.16	"	0922	0922			
	0.25	"	0927	0927	#60		
	0.33	"	0932	0932			
	0.42	"	0937	0937			
	0.50	"	0942	0942	#48	#ND	#ok
	0.58	"	0947	0947			
	0.66	"	0952	0952			
	0.75	"	0957	0957	#48		
	0.83	"	1002	1002			
	0.92	"	1007	1007			
	1.0	"	1012	1012	#56	#ND	
	1.33	"	1032		#50		
	1.66	"	1052		#52		
	2.0	"	1112		#60	#ND	
	2.5	"	1142				

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J A H F M L	015-	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21Jan86	0912	0942	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J A M F M L	015	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0810	0810	PO	NA

syringe + pyrido = 7.60 g
syringe - pyrido = 5.94 g

DOSAGE (total) 16 mg**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	24 JAN 86	0807	0807	B28: *	B59: 14.29
B29, B60	0.25	"	0825	0825	B29: *	B60: 14.07
B30, B61	0.50	"	0840	0840	B30: *	B61: 14.16
B31, B62	0.75	"	0855	0855	B31: 5.4	B62: 13.48
B32, B63	1.0	"	0910	0910	B32: 7.83	B63: 12.29
B33, B64	1.33	"	0930	0930	B33: 10.9	B64: 11.16
B34, B65	1.66	"	0950	0950	B34: 4.6	B65: 10.50
B35, B66	2.0	"	1010	1010	B35: 12.3	B66: 9.53
B36	2.5	"	1040	1040	B36: 10.9	
B37, B67	3.0	"	1110	1110	B37: 13.5	B67: 8.77
B38	3.5	"	1140	1140	B38: 12.0	
B39, B68	4.0	"	1210	1210	B39: 13.2	B68: 9.11
B40	5.0	"	1310	1310	B40: 11.5	
B41, B69	6.0	"	1410	1410	B41: 6.22	B69: 11.21
B42	7.0	"	1510	1510	B42: 2.56	
B43	8.0	"	1610	1610	B43: *	B69A: 12.74
B44	10.0	"	1810	1810	B44: *	13.32

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J</u> <u>A</u> <u>H</u> <u>F</u> <u>M</u> <u>L</u>	015-	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0810	0810	PO	

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> <u>F M L</u>	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 84	0810	0810	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	24 JAN 84	0807	0807	# 50	# ND	# OK
	0.25	"	0825	0807	# 52		-
	0.50	"	0840	0840	# 50	# ND	# OK
	0.75	"	0855	0855	# 60		
	1.0	"	0910	0910	# 60	# ND	
	1.33	"	0930	0930	# 64		
	1.66	"	0950	0950	# 60		
	2.00	"	1010	1010	# 64	# ND	
	2.5	"	1040	1040			
	3.0	"	1110	1110	# 60		
	3.5	"	1140	1140			
	4.0	"	1210	1210	# 64	# ND	
	5.0	"	1310	1310			
	6.0	"	1410	1410	# 68	# ND	
	7.0	"	1510	1510			
	8.0	"	1610	1610			
	10.0	"	1810	1810			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> F M L	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES
Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST:NORMAL	<u>08 JAN 86</u> ddmmmyy	<u>20 JAN 86</u> ddmmmyy	<u>21 JAN 86</u> ddmmmyy	<u>22 JAN 86</u> ddmmmyy	<u>24 JAN 86</u> ddmmmyy
NA:135-148 MEQ/L	140	152		140	
K:3.5-5.0 MEQ/L	4.3	4.3		4.1	
CL:96-109 MEQ/L	104	116		106	
CO2:24-30 MEQ/L	26	27		28	
SUN:12-25 MG/DL	17	11		13	
CREAT:0.4-1.5 MG/DL	1.0	1.1		1.1	
GLU:70-115 MG/DL	83	97		82	
T. BILI:0.3-1.2MG/DL	ND	0.9		1.0	
D. BILI:0.1-0.4MG/DL	0.1	0.1		0.0	
CA:9.0-11.0 MG/DL	10.2	10.3		9.8	
PO4:3.0-4.5 MG/DL	4.2	3.6		4.0	
URIC A:4.2-8.8MG/DL	5.2	7.2		6.4	
T. PROT:6.0-8.5G/DL	7.3	7.1		6.8	
ALB.:3.2-5.3 G/DL	4.7	4.6		4.5	
AST:0-35 IU/L	17	27		19	
ALT:0-30 IU/L	13	11		6	
ALK PHOS:0-95 IU/L	65	58		51	
CHOL:151-268 MG/DL	173	183		185	
LDH:0-200 IU/L	ND	140		123	
CPK:0-160 U/L (male)	ND	739	262	171	125

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J A H F M L	015	Pyridostigmine
			PROTOCOL
			DAMD 17-85-C-5133-02

CHEMISTRY VALUES
Laboratory

Johns Hopkins Hospital

	Screen	Predrug		Study
TEST: NORMAL	NA ddmmmyy	NA ddmmmyy	25 JAN 86 ddmmmyy	Date
NA: 135-148 MEQ/L			137	
K: 3.5-5.0 MEQ/L			4.0	
CL: 96-109 MEQ/L			103	
CO2: 24-30 MEQ/L			25	
SUN: 12-25 MG/DL			12	
CREAT: 0.4-1.5 MG/DL			1.1	
GLU: 70-115 MG/DL			72	
T. BILI: 0.3-1.2 MG/DL			1.2	
D. BILI: 0.1-0.4 MG/DL			0.0	
CA: 9.0-11.0 MG/DL			9.7	
PO4: 3.0-4.5 MG/DL			4.3	
URIC A: 4.2-8.8 MG/DL			5.9	
T. PROT: 6.0-8.5 G/DL			6.9	
ALB.: 3.2-5.3 G/DL			4.5	
AST: 0-35 IU/L			14	
ALT: 0-30 IU/L			14	
ALK PHOS: 0-95 IU/L			48	
CHOL: 151-268 MG/DL			203	
LDH: 0-200 IU/L			ND	
CPK: 0-160 U/L (male)			105	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A H</u> F M L	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen	Predrug	Study Date		
TEST	NORMAL	28 JAN 86 ddmmmyy	29 JAN 86 ddmmmyy	31 JAN 86 ddmmmyy	22 JAN 86 ddmmmyy	24 JAN 86 ddmmmyy
Hgb	13.9-16.3	15.3	14.3		14.6	13.8
PCV	41.0-53.0	43.8	41.1		42.1	40.3
Plt	150-350	287	280		280	262
RBC	4.50-5.90	4.75	4.46		4.52	4.29
WBC	4500-11000	5300	5000		4900	4000
Bands	2-6%	6	6		1	7
Polys	31-76%	51	46		51	44
Eos	1-4%	3	0		1	1
Bas		0	0		0	0
Lymphs	24-44%	35	43		46	41
Atyp Lym		1	0		0	0
Monos	2-11%	4	5		1	7
Other		0	0		0	0
Retics	0.5-1.5%	ND	ND	N.D. 2.2		2.2

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J A M</u> <u>F M L</u>	<u>015</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	15 JAN 86 ddmmmyy	21 JAN 86 ddmmmyy	22 JAN 86 ddmmmyy	25 JAN 86 ddmmmyy	Date ddmmmyy
Color/Sp		clear	clear	clear	ND	
Sp. Gr.		1.017	1.024	1.017	1.020	
pH		5.0	6.0	5.0	7.0	
Protein		neg	neg	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		0	none	0	1	
Casts		0	0	0	0	
Epi. Cel		0	0	0	0	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
15 JAN 86		✓	non-specific ST-T changes. ^{tracing} E min change between tracings
22 JAN 86		✓	non-specific ST-T changes. ^{tracing} E min change between tracings
25 JAN 86		✓	non-specific ST-T changes. ^{tracing} E min change between tracings

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J R H</u> F M L	<u>05</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>L</u> <u>A</u> <u>F</u> <u>M</u> <u>L</u>	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	20 JAN 86 21 JAN 86	Screening laboratory
—		History, Physical Exam
0	20 JAN 86	Admission
2	21 JAN 86	IV
5	24 JAN 86	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 016.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt Petty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D L A</u> F M L	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 01/15/86
dd mm yy

Examiner Brent G. Petty, M.D.

Date of birth 09/29/58
dd mm yy

Brent G. Petty, M.D.
print name

Age 27 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	1/2 ppd
Alcohol Use		✓	1 pint brandy / week
Recreational Drug Use		✓	Cocaine, last 3 wks MIS 1/week
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Pharmakinetos - July 85, Umed 9/85, Ceftriaxime supp 12/85
Blood or plasma donor		✓	last Oct 1985
Prior Surgery		✓	Umbilical hernia repair age 4
Eye, ear, nose, throat		✓	Glasses x 15 yrs
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		diarrhea c ceftriaxime suppository 2 days
Genito-urinary		✓	GC 9th grade
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
<u>Lietman</u>	<u>D L A</u> <u>F M L</u>	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/15/86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.2C</u>	<u>84/min</u>	<u>16/min</u>	<u>126/88</u>	<u>196.0</u>	<u>104.8</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck		✓	large scar @ neck from trauma 1983
EENT		✓	Gold earring (pierced) @ earlobe
Chest, lungs	✓		1 cm cyp just @ low thoracic spine--
Heart	✓		
Abdomen	✓		Umbilical herniorrhaphy scar
Genitalia	ND		
Rectal	ND		
Extremities		✓	scar medial aspect @ foot, superiorly
Skin	✓		
Neurologic	✓		

CHEST X-RAY

Date 15/ JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL	<input type="checkbox"/>	Describe abnormalities:

Examiner

Brent G. Petty MD
BRENT G. Petty, M.D.
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>L</u> <u>A</u> <u>F</u> <u>M</u> <u>L</u>	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 JAN 86	0916	0946	IV	NA

Syringe + pyrido 43.42423
 Syringe - pyrido 23.16032

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	21 JAN 86	0815	0815	B01: *	B47: 12.64
B02	0.08	"	0921	0921	B02: 7.83	
B03	0.16	"	0926	0926	B03: 10.9	
B04, B48	0.25	"	0931	0931	B04: 14.2	B48: 10.54
B05	0.33	"	0936	0936	B05: 14.6	
B06	0.42	"	0941	0941	B06: 19.4	
B07, B49	0.50	"	0946	0945	B07: 21.0	B49: 9.35
B08	0.58	"	0951	0951	B08: 11.0	
B09	0.66	"	0956	0956	B09: 8.64	
B10, B50	0.75	"	1001	1001	B10: 10.7	B50: 9.55
B11	0.83	"	1006	1006	B11: 7.20	
B12	0.92	"	1011	1011	B12: 5.83	
B13, B51	1.0	"	1016	1016	B13: 5.85	B51: 10.21
B14, B52	1.33	"	1036	1036	B14: 2.63	B52: 10.98
B15, B53	1.66	"	1056	1056	B15: 1.67	B53: 11.14
B16, B54	2.0	"	1116	1116	B16: *	B54: 11.20
B17	2.5	"	1146	1146	B17: 2.05	

* below assay sensitivity 371

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\begin{array}{c} D \\ F \end{array} \begin{array}{c} L \\ M \end{array} \begin{array}{c} A \\ L \end{array}$	016	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 JAN 86	0916	0946	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B18, B55	3.0	21 JAN 86	1216	1216	B18: *	B55: 11.26
B19	3.5	"	1246	1246	B19: *	
B20, B56	4.0	"	1316	1316	B20: *	B56: 12.50
B21	5.0	"	1416	1416	B21: *	
B22, B57	6.0	"	1516	1516	B22: *	B57: 12.51
B23	7.0	"	1616	1616	B23: *	
B24	8.0	"	1716	1716	B24: *	
B25	10.0	"	1916	1916	B25: *	
B26	12.0	"	2116	2116	B26: *	
B27, B58	24.0	22 JAN 86	0916	0916	B27: *	B58: 12.28

* below assay sensitivity 372

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	016	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 JAN 86	0916	0946	IV	NA

DOSAGE (total) 1.32mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	21 JAN 86	0815	0815	# 70	# ND	# OK
	0.8	"	0921	0921			
	0.16	"	0926	0926			
	0.25	"	0931	0931	# 60		
	0.33	"	0936	0936			
	0.42	"	0941	0941			
	0.50	"	0946	0946	# 70	# ND	# OK
	0.58	"	0951	0951			
	0.66	"	0956	0956			
	0.75	"	1001	1001	# 74		
	0.83	"	1006	1006			
	0.92	"	1011	1011			
	1.0	"	1016	1016	# 80	# ND	
	1.33	"	1036	1036	# 78		
	1.66	"	1056	1056	# 72		
	2.0	"	1116	1116	# 72	# ND	
	2.5	"	1146	1146			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>L</u> <u>A</u> <u>F</u> <u>M</u> <u>L</u>	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	21 JAN 86	0916	0946	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D L A</u> <u>F M L</u>	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0813	0813	PO	NA

syringe + pyridos = 7.54g
syringe - pyridos = 5.90g

DOSAGE (total) 16 mg.**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	24 JAN 86	0810	0810	B28: *	B59: 12.70
B29, B60	0.25	"	0828	0828	B29: *	B60: 12.63
B30, B61	0.50	"	0843	0843	B30: *	B61: 12.72
B31, B62	0.75	"	0858	0858	B31: *	B62: 12.83
B32, B63	1.0	"	0913	0913	B32: *	B63: 12.82
B33, B64	1.33	"	0933	0933	B33: 167	B64: 12.45
B34, B65	1.66	"	0953	0953	B34: 375	B65: 11.84
B35, B66	2.0	"	1013	1013	B35: 10.2	B66: 10.96
B36	2.5	"	1043	1043	B36: 5.90	
B37, B67	3.0	"	1113	1113	B37: 4.96	B67: 10.14
B38	3.5	"	1143	1143	B38: 5.30	
B39, B68	4.0	"	1213	1213	B39: 7.53	B68: 10.24
B40	5.0	"	1313	1313	B40: 7.02	
B41, B69	6.0	"	1413	1413	B41: 6.28	B69: 10.17
B42	7.0	"	1513	1513	B42: 4.61	
B43	8.0	"	1613	1613	B43: 3.57	B69A: 10.90
B44	10.0	"	1813	1813	B44: 2.20	11.74

* below assay sensitivity 375

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>L</u> <u>A</u> <u>F</u> <u>M</u> <u>L</u>	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0813	0813	PO	NA

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0813	0813	PO	NA

DOSAGE (total) 16mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	24 JAN 86	0810	0810	#80	#ND	#OK
	0.25	"	0828	0828	#70		-
	0.50	"	0843	0843	#77	#ND	#OK
	0.75	"	0858	0858	#80		
	1.0	"	0913	0913	#80	#ND	
	1.33	"	0933	0933	#80		
	1.66	"	0953	0953	#84		
	2.00	"	1013	1013	#76	#ND	
	2.5	"	1043	1043			
	3.0	"	1113	1113	#72		
	3.5	"	1143	1143			
	4.0	"	1213	1213	#76	#ND	
	5.0	"	1313	1313			
	6.0	"	1413	1413	#90	#ND	
	7.0	"	1513	1513			
	8.0	"	1613	1613			
	10.0	"	1813	1813			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	24 JAN 86	0813	0813	PO	NA

DOSAGE (total) 16 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	816	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

CHEMISTRY VALUES
Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	20 JAN 86 ddmmmyy	21 JAN 86 ddmmmyy	22 JAN 86 ddmmmyy	24 JAN 86 ddmmmyy	Date
NA: 135-148 MEQ/L	142	141		138	
K: 3.5-5.0 MEQ/L	5.1	4.5		3.9	
CL: 96-109 MEQ/L	107	105		105	
CO2: 24-30 MEQ/L	29	24		24	
SUN: 12-25 MG/DL	14	14		12	
CREAT: 0.4-1.5 MG/DL	1.2	0.9		1.0	
GLU: 70-115 MG/DL	93	83		153	
T. BILI: 0.3-1.2 MG/DL	0.6	0.7		0.7	
D. BILI: 0.1-0.4 MG/DL	0.1	0.0		0.1	
CA: 9.0-11.0 MG/DL	10.6	9.9		10.1	
PO4: 3.0-4.5 MG/DL	3.3	3.6		3.6	
URIC A: 4.2-8.8 MG/DL	6.1	5.4		5.6	
T. PROT: 6.0-8.5 G/DL	7.7	7.4		7.3	
ALB.: 3.2-5.3 G/DL	4.6	4.3		4.5	
AST: 0-35 IU/L	21	22		21	
ALT: 0-30 IU/L	21	23		14	
ALK PHOS: 0-95 IU/L	44	43		43	
CHOL: 151-268 MG/DL	200	191		188	
LDH: 0-200 IU/L	145	140	145	147	155
CPK: 0-160 U/L (male)	ND	238	227	182	208

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D L A</u> <u>F M L</u>	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NA</u> ddmmyy	<u>NA</u> ddmmyy	<u>25 JAN 86</u> ddmmyy	ddmmyy	ddmmyy	Date
NA: 135-148 MEQ/L			140			
K: 3.5-5.0 MEQ/L			4.1			
CL: 96-109 MEQ/L			101			
CO2: 24-30 MEQ/L			29			
SUN: 12-25 MG/DL			12			
CREAT: 0.4-1.5 MG/DL			1.1			
GLU: 70-115 MG/DL			86			
T. BILI: 0.3-1.2 MG/DL			0.7			
D. BILI: 0.1-0.4 MG/DL			0.1			
CA: 9.0-11.0 MG/DL			10.0			
PO4: 3.0-4.5 MG/DL			3.6			
URIC A: 4.2-8.8 MG/DL			5.5			
T. PROT: 6.0-8.5 G/DL			7.8			
ALB.: 3.2-5.3 G/DL			4.7			
AST: 0-35 IU/L			19			
ALT: 0-30 IU/L			13			
ALK PHOS: 0-95 IU/L			42			
CHOL: 151-268 MG/DL			195			
LDH: 0-200 IU/L			143			
CPK: 0-160 U/L (male)			248			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	016	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital
University Clinical Pharmacology

TEST	NORMAL	Screen Predrug	Pre-drug Screen	Study Date		
		20 JAN 86 ddmmmyy	21 JAN 86 ddmmmyy	22 JAN 86 ddmmmyy	24 JAN 86 ddmmmyy	25 JAN 86 ddmmmyy
Hgb	13.9-16.3	14.7		14.6		14.7
PCV	41.0-53.0	43.4		43.3		42.6
Plt	150-350	303		285		297
RBC	4.50-5.90	4.9		4.9		4.87
WBC	4500-11000	6900		6000		7300
Bands	2-6%	3		1		5
Polys	31-76%	21		31		27
Eos	1-4%	4		6		5
Bas		1		0		0
Lymphs	24-44%	65		57		52
Atyp Lym		0		3		1
Monos	2-11%	6		2		10
Other		0		0		0
Retics	0.5-1.5%	N.D.		N.D.		1.2

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{D}{F} \frac{L}{M} \frac{A}{L}$	016	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	15 JAN 86 ddmmmyy	21 JAN 86 ddmmmyy	22 JAN 86 ddmmmyy	25 JAN 86 ddmmmyy	----- ddmmmyy	Date
Color/Sp		clear	yellow	yellow	not recorded		
Sp. Gr.		1.021	1.020	1.019	1.028		
pH		7.0	6.0	6.0	5.0		
Protein		TRACE	TRACE	neg	neg		
Ketones		neg	neg	neg	neg		
Occ Bld		neg	neg	neg	neg		
Bili.		neg	neg	neg	neg		
RBC		0	0	0	0		
WBC		0	0	0	0-1		
Casts		0	0	0	0		
Epi. Cel		0	0	0	0		
Crystals		0	0	0	0		
Bacteria		0	0	0	0		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
15 Jan 86	✓		
22 Jan 86	✓		
25 Jan 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>L</u> <u>A</u> <u>F</u> <u>M</u> <u>L</u>	<u>016</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E</u> <u>-</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	<u>017</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	17 JAN 86	Screening laboratory
—	22 JAN 86	History, Physical Exam
0	26 JAN 86	Admission
2	28 JAN 86	IV
5	30 JAN 86	ORAL

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 017.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E - W</u> <u>F M L</u>	<u>017</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 23 JAN 86 (55)

Examiner

Brent G. Petty, M.D.

Date of birth

26 JAN 64
(4) 26 JAN 64
dd mmm yy

BRENT G. PETTY, M.D.
print name

Age

21 yrs

Sex

M

Race

B

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1 ppd
Alcohol Use		✓	6 pack/week
Recreational Drug Use		✓	marijuana 4 month
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	JHU-Ibuprofen, Ceftriaxone
Blood or plasma donor	✓		
Prior Surgery		✓	MVA & lacerations 1971
Eye, ear, nose, throat	✓		URI last week
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)		✓	Smoker's cough
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC 1982
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E - W</u> <u>F M L</u>	<u>017</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 27 JAN 1986
 dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>N.D.</u> C	<u>64</u> /min	<u>16</u> /min	<u>124</u> / <u>82</u>	<u>174.0</u>	<u>65.5</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		
Chest, lungs		✓	Deformity of chest wall at R 2nd intercostal articulation
Heart	✓		
Abdomen	✓		
Genitalia	<u>ND</u>		
Rectal	<u>ND</u>		
Extremities	✓		
Skin		✓	Tattoos (C) chest, (L) arm, (L) hand; scars (R) medial knee, (C) eyebrow, above (L) eye.
Neurologic	✓		

CHEST X-RAY

Date 20/NOV/85

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty, M.D.
Brent G. Petty, M.D.
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	E - - W F M L	017	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	27 JAN 86	0835	0905	IV	NA

Syringe + pyridos = 42.69
 Syringe + pyridos = 22.68

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

subject's wt: 71.6 kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	REC ACHe uM/ml/min
B01, B47	0	27 JAN 86	0805	0805	B01: *	B47: 15.73
B02	0.08	"	0840	0840	B02: 8.87	
B03	0.16	"	0845	0845	B03: 6.17	
B04, B48	0.25	"	0850	0850	B04: 12.9	B48: 13.17
B05	0.33	"	0855	0855	B05: 14.2	
B06	0.42	"	0900	0900	B06: 16.2	
B07, B49	0.50	"	0905	0905	B07: 20.7	B49: 11.12
B08	0.58	"	0910	0910	B08: 10.1	
B09	0.66	"	0915	0915	B09: 8.92	
B10, B50	0.75	"	0920	0920	B10: 6.16	B50: 11.96
B11	0.83	"	0925	0925	B11: 5.22	
B12	0.92	"	0930	0930	B12: 3.82	
B13, B51	1.0	"	0935	0935	B13: 3.10	B51: 12.75
B14, B52	1.33	"	0955	0955	B14: 2.29	B52: 13.78
B15, B53	1.66	"	1015	1015	B15: 1.71	B53: 14.31
B16, B54	2.0	"	1035	1035	B16: *	B54: 14.64
B17	2.5	"	1105	1105	B17: *	

* below assay sensitivity 387

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	$\frac{E}{F} - \frac{W}{M L}$	47	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	27 JAN 86	0835	0905	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	27 JAN 86	1135 1135 error	1135	B18: *	B55: 15.06
B19	3.5	"	1205	1205	B19: *	
B20, B56	4.0	"	1235	1235	B20: NR	B56: 15.28
B21	5.0	"	1335	1335	B21: *	
B22, B57	6.0	"	1435	1435	B22: *	B57: 15.69
B23	7.0	"	1535	1535	B23: *	
B24	8.0	"	1635	1635	B24: *	
B25	10.0	"	1835	1835	B25: *	
B26	12.0	"	2035	2035	B26: *	
B27, B58	24.0	28 JAN 86	0835	0835	B27: *	B58: 15.33

* below assay sensitivity N.R. = not run

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{E}{F} - \frac{U}{M} - \frac{L}{L}$ 017		Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	27 JAN 86	0835	0905	IV	NA

DOSAGE (total) 1.32 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	27 JAN 86	0805	0805	# 50	# ND	# OK
	0.8	"					
	0.16	"					
	0.25	"	0850	0850	# 50		
	0.33	"					
	0.42	"					
	0.50	"	0905	0905	# 52	# ND	# OK
	0.58	"					
	0.66	"					
	0.75	"	0920	0920	# 60		
	0.83	"					
	0.92	"					
	1.0	"	0935	0935	# 64	# ND	
	1.33	"	0955	0955	# 70		
	1.66	"	1015	1015	# 64		
	2.0	"	1035	1035	# 64	# ND	
	2.5	"					

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E - W</u> <u>F M L</u>	<u>017</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>2</u>	<u>27 JAN 86</u>	<u>0835</u>	<u>0905</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	<u>27 JAN 86</u>	<u>1135</u>		<u>#64</u>		
	3.5	<u>"</u>					
	4.0	<u>"</u>	<u>1235</u>		<u>#64</u>	<u># ND</u>	
	5.0	<u>"</u>					
	6.0	<u>"</u>	<u>1435</u>		<u>#60</u>	<u># ND</u>	
	7.0	<u>"</u>					
	8.0	<u>"</u>					
	10.0	<u>"</u>					
	12.0	<u>"</u>					
	24.0	<u>28 JAN 86</u>	<u>0835</u>		<u>#56</u>	<u># ND</u>	<u># OK</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{matrix} E & - & W \\ F & M & L \end{matrix}$	017	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	30 JAN 86	0855	0855	PO	7A

Syringe + pyrid = 7.63947
 Syringe - pyrid = 5.95118

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	30 JAN 86	0840	0840	B28: *	B59: 15.39
B29, B60	0.25	"	0910	0910	B29: *	B60: 15.62
B30, B61	0.50	"	0925	0925	B30: 7.75	B61: 14.06
B31, B62	0.75	"	0940	0940	B31: 10.6	B62: 12.64
B32, B63	1.0	"	0955	0955	B32: 11.1	B63: 11.90
B33, B64	1.33	"	1015	1015	B33: 13.8	B64: 10.96
B34, B65	1.66	"	1035	1035	B34: 10.2	B65: 10.64
B35, B66	2.0	"	1055	1055	B35: 10.5	B66: 10.73
B36	2.5	"	1125	1125	B36: 9.42	
B37, B67	3.0	"	1155	1155	B37: 8.37	B67: 11.10
B38	3.5	"	1225	1230	B38: 6.28	
B39, B68	4.0	"	1255	1255	B39: 6.53	B68: 11.43
B40	5.0	"	1355	1405	B40: 4.69	
B41, B69	6.0	"	1455	1455	B41: 3.52	B69: 13.44
B42	7.0	"	1555	1555	B42: *	
B43	8.0	"	1655	1655	B43: *	B69A: 14.06
B44	10.0	"	1855	1855	B44: *	14.70

* below assay sensitivity 391

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{E}{F} - \frac{W}{M L}$	017	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	30 Nov 81	0855	0855	PO	RA

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{array}{c} E \\ \hline F \end{array} \begin{array}{c} - \\ \hline M \end{array} \begin{array}{c} W \\ \hline L \end{array}$	017	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	30 Jan 86	0855	0855	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	30 Jan 86	0855	0855	# 45	# ND	# OK
	0.25	"	0910	0910	# 48		-
	0.50	"	0925	0925	# 40	# ND	# OK
	0.75	"	0940	0940	# 68		
	1.0	"	0955	0955	# 64	# ND	
	1.33	"	1015	1015	# 60		
	1.66	"	1035	1035	# 56		
	2.00	"	1055	1055	# 60	# ND	
	2.5	"	1125	1125			
	3.0	"	1155	1155	# 64		
	3.5	"	1225	1225			
	4.0	"	1255	1255	# 60	# ND	
	5.0	"	1355	1355			
	6.0	"	1455	1455	# 60	# ND	
	7.0	"	1555	1555			
	8.0	"	1655	1655			
	10.0	"	1855	1855			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E - W</u> <u>F M L</u>	<u>017</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	<u>17 Jan 86</u> ddmmyy	<u>26 Jan 86</u> ddmmyy	<u>28 Jan 86</u> ddmmyy	<u>27 Jan 86</u> ddmmyy	<u>31 Jan 86</u> ddmmyy
NA:135-148 MEQ/L	140	ND	140		141
K:3.5-5.0 MEQ/L	4.4	ND	4.7		4.7
CL:96-109 MEQ/L	104	ND	108		102
CO2:24-30 MEQ/L	24	ND	19		30
SUN:12-25 MG/DL	16	17	15		16
CREAT:0.4-1.5 MG/DL	0.9	1.2	0.9		1.0
GLU:70-115 MG/DL	82	97	88		116
T. BILI:0.3-1.2MG/DL	1.2	0.7	0.6		0.9
D. BILI:0.1-0.4MG/DL	—	0.1	0.0		0.1
CA:9.0-11.0 MG/DL	9.7	9.6	8.9		9.7
PO4:3.0-4.5 MG/DL	4.1	4.2	4.2		3.6
URIC A:4.2-8.8MG/DL	4.8	5.2	4.0		4.9
T. PROT:6.0-8.5G/DL	6.6	7.1	—		7.0
ALB.:3.2-5.3 G/DL	4.9	4.7	4.3		4.9
AST:0-35 IU/L	11	34	22		17
ALT:0-30 IU/L	4	16	8		13
ALK PHOS:0-95 IU/L	49	48	45		45
CHOL:151-268 MG/DL	219	212	186		227
LDH:0-200 IU/L	—	167	179	172	—
CPK:0-160 U/L (male)	—	482	270	362	—

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND Pyridostigmine
Lietman	$\frac{E}{F} - \frac{W}{M} \frac{L}{L}$	017	PROTOCOL DAMD 17-85-C-5133-02

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

		Screen	Predrug	Study	
		17 Jan 86	26 Jan 86	28 Jan 86	31 Jan 86
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy
Hgb	13.9-16.3	14.1	15.5	14.5	15.5
PCV	41.0-53.0	41.7	45.3	42.5	45.3
Plt	150-350	343	218	186	364
RBC	4.50-5.90	4.57	5.07	4.75	5.13
WBC	4500-11000	6000	4200	4200	4700
Bands	2-6%	3	0	9	3
Polys	31-76%	42	41	40	39
Eos	1-4%	2	0	4	6
Bas		1	0	1	1
Lymphs	24-44%	47	40	36	48
Atyp Lym		0	2	1	0
Monos	2-11%	5	17	9	3
Other		0	0	0	0
Retics	0.5-1.5%	N.D.	N.D.	N.D.	N.D.

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{E}{F} - \frac{M}{L}$	017	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

TEST	NORMAL	Screen	Predrug	Study			Date
		22 Jan 86	28 Jan 86	31 Jan 86	-----	-----	
		ddmmyy	ddmmyy	ddmmyy	ddmmyy	ddmmyy	
Color/Sp		clear	yellow	cloudy			
Gr.		1.020	1.022	1.019			
pH		7.0	6.5	6.0			
Protein		neg	+ neg	neg			
Ketones		neg	neg	neg			
Occ Bld		neg	neg	neg			
Bili.		neg	neg	neg			
RBC		0	0	0			
WBC		0	0	0			
Casts		0	0	0			
Epi. Cel		0	0	0			
Crystals		0	0	0			
Bacteria		0	0	0			

ELECTROCARDIOGRAM

Date	NORMAL	ABNORMAL	Describe abnormalities
ddmmyy	check	check	
22 Jan 86	✓		
28 Jan 86	✓		
31 Jan 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>E</u> <u>-</u> <u>W</u> <u>F</u> <u>M</u> <u>L</u>	<u>017</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		____ _ dd mm yy	____ _ dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		____ _ dd mm yy	____ _ dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H K F M L	018	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	21 JAN 86	Screening laboratory
—	22 JAN 86	History, Physical Exam
0	26 JAN 86	Admission
2	27 JAN 86	IV
5	30 JAN 86	ORAL

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 018.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24, Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H L</u> F M L	<u>018</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 22 JAN 86
21 / 2 / 86
 dd mm yy

Examiner

Brent G. Petty, M.D.
BRENT G. PETTY, M.D.
 print name

Date of birth 11 JAN 63
 dd mm yy

Age 22 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	1 1/2 ppd
Alcohol Use		✓	1 6 pack / week
Recreational Drug Use		✓	MJ @ 4 weeks, last month ago
Medications past 2 weeks		✓	Tylenol ~ 2 d ago for HA
Experimental Drug Exposure		✓	Tobramycin
Blood or plasma donor		✓	Volunteer blood donor at hospital
Prior Surgery		✓	Repair of hypospadias age 4 - had bilateral pneumothorax @ d 1/2 chest tube
Eye, ear, nose, throat		✓	Wears glasses
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	2 dogs & baths for fleas today
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H U</u> F M L	<u>818</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 22 Jan 86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>36.8</u> C	<u>88</u> /min	<u>20</u> /min	<u>120 / 82</u>	<u>192.0</u>	<u>78.8</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		Shotty node (R) SC area
EENT		✓	Sclerotic TM's bilaterally, Nasal septum deviated to (L). Discoloration betw top front teeth.
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		not	
Rectal		not	
Extremities	✓		
Skin		✓	Tattoo (R) shoulder & (L) forearm, scars anterior chest bilaterally from chest tube placements, scars (L) forearm, small laceration (R) proximal thumb
Neurologic	✓		

CHEST X-RAY

Date 22 Jan 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty, M.D.
BRENT G. PETTY, M.D.
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H L</u> F M L	018	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	27 Jun 86	0838	1.35 0908	IV	NA

Syringe + pyrid = 42.43g
 Syringe - pyrid = 22.47g

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	27 Jun 86	0805	0805	B01: *	B47: 13.41
B02	0.08	"	0842	0842	B02: 6.90	B48
B03	0.16	"	0848 ^{SS}	0848 ^{SS}	B03: 10.5	
B04, B48	0.25	"	0853 ^{SS}	0853 ^{SS}	B04: 12.3	B48 B 11.77
B05	0.33	"	0858 ^{SS}	0858 ^{SS}	B05: 12.9	
B06	0.42	"	0903 ^{SS}	0903 ^{SS}	B06: 20.6	
B07, B49	0.50	"	0908 ^{SS}	0908 ^{SS}	B07: 18.9	B49: 10.41
B08	0.58	"	0913	0913	B08: 14.5	
B09	0.66	"	0918	0918	B09: 10.5	
B10, B50	0.75	"	0923	0923	B10: 5.67	B50: 10.82
B11	0.83	"	0928	0928	B11: 5.50	
B12	0.92	"	0933	0933	B12: 4.61	
B13, B51	1.0	"	0938	0938	B13: 4.37	B51: 11.47
B14, B52	1.33	"	0958	0958	B14: 3.19	B52: 12.04
B15, B53	1.66	"	1018	1018	B15: 2.34	B53: 12.65
B16, B54	2.0	"	1038	1038	B16: *	B54: 12.80
B17	2.5	"	1108	1108	B17: *	

* below assay sensitivity 402

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>U</u> F <u>H</u> M <u>L</u>	<u>018</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>2</u>	<u>27 Jan 86</u>	<u>0838</u>	<u>0908</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	<u>22 Jan 86</u>	<u>1138</u>	<u>1138</u>	B18: *	B55: <u>12.78</u>
B19	3.5	<u>"</u>	<u>1208</u>	<u>1208</u>	B19: *	
B20, B56	4.0	<u>"</u>	<u>1238</u>	<u>1238</u>	B20: *	B56: <u>13.41</u>
B21	5.0	<u>"</u>	<u>1338</u>	<u>1338</u>	B21: *	
B22, B57	6.0	<u>"</u>	<u>1438</u>	<u>1438</u>	B22: *	B57: <u>13.40</u>
B23	7.0	<u>"</u>	<u>1538</u>	<u>1538</u>	B23: *	
B24	8.0	<u>"</u>	<u>1638</u>	<u>1638</u>	B24: *	
B25	10.0	<u>"</u>	<u>1838</u>	<u>1838</u>	B25: *	
B26	12.0	<u>"</u>	<u>2038</u>	<u>2038</u>	B26: *	
B27, B58	24.0	<u>28 Jan 86</u>	<u>0838</u>	<u>0838</u>	B27: *	B58: <u>13.30</u>

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	W-H-L F-M-L	018	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	27 Jan 86	0838	0908	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmmy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	27 Jan 86	0805	0805	#70	# ND	# OK
	0.8						
	0.16						
	0.25	"	0853	0853	#68		
	0.33						
	0.42						
	0.50	"	0908	0908	#78	# ND	# OK
	0.58						
	0.66						
	0.75	"	0923	0923	#70		
	0.83						
	0.92						
	1.0	"	0938	0938	#80	# ND	
	1.33	"	0958	0958	#76		
	1.66	"	1018	1018	#82		
	2.0	"	1038	1038	#76	# ND	
	2.5						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>U</u> F M L	<u>018</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>2</u>	<u>27 Jan 86</u>	<u>0838</u>	<u>0908</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	<u>27 Jan 86</u>	<u>1138</u>	<u>1138</u>	<u># 70</u>		
	3.5	<u>4</u>					
	4.0	<u>11</u>	<u>1238</u>	<u>1238</u>	<u># 76</u>	<u># ND</u>	
	5.0	<u>11</u>					
	6.0	<u>11</u>	<u>1438</u>	<u>1438</u>	<u># 72</u>	<u># ND</u>	
	7.0	<u>11</u>					
	8.0	<u>11</u>					
	10.0	<u>11</u>					
	12.0	<u>11</u>					
	24.0	<u>28 Jan 86</u>	<u>0838</u>	<u>0838</u>	<u># 70</u>	<u># ND</u>	<u># OK</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H U</u> F M L	018	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	30 Jan 86	0900	0900	PO	NA

Syringe + pyrido = 7.63564
 Syringe - pyrido = 5.94243

DOSAGE (total) 16 mg

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	30 Jan 86	0843	0843	B28: *	B59: 13.45
B29, B60	0.25	"	0915	0915	B29: *	B60: 13.35
B30, B61	0.50	"	0930	0930	B30: 8.04	B61: 12.28
B31, B62	0.75	"	0945	0945	B31: 17.9	B62: 10.99
B32, B63	1.0	"	1000	1000	B32: 14.8	B63: 10.72
B33, B64	1.33	"	1020	1020	B33: 11.8	B64: 10.48
B34, B65	1.66	"	1040	1040	B34: 11.9	B65: 10.65
B35, B66	2.0	"	1100	1100	B35: 7.74	B66: 10.73
B36	2.5	"	1130	1130	B36: 6.01	
B37, B67	3.0	"	1200	1200	B37: 5.26	B67: 11.12
B38	3.5	"	1230	1230	B38: 4.28	
B39, B68	4.0	"	1300	1300	B39: 3.45	B68: 11.42
B40	5.0	"	1400	1400	B40: 3.06	
B41, B69	6.0	"	1500	1500	B41: *	B69: 12.18
B42	7.0	"	1600	1600	B42: *	
B43	8.0	"	1700	1700	B43: *	B69A: 13.03
B44	10.0	"	1900	1900	B44: *	13.22

* below assay sensitivity 406

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H U F M L	018	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	30 Jan 86	0902	0950	PO	72A

DOSAGE (total) 16 mg

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H L F M L	18	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	30 June 86	0900	0900	PO	NA

DOSAGE (total) 16 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0			0900	# 72	# ND	# OK
	0.25			0915	# 70		-
	0.50			0930	# 72	# ND	# OK
	0.75			0945	# 80		
	1.0			1000	# 78	# ND	
	1.33			1020	# 80		
	1.66			1040	# 80		
	2.00			1100	# 76	# ND	
	2.5						
	3.0			1200	# 84		
	3.5						
	4.0			1300	# 80	# ND	
	5.0						
	6.0			1500	# 80	# ND	
	7.0						
	8.0						
	10.0						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	W H U F M L	018	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	21 Jan 86 ddmmmyy	26 Jan 86 ddmmmyy	27 Jan 86 ddmmmyy	28 Jan 86 ddmmmyy	31 Jan 86 ddmmmyy
NA: 135-148 MEQ/L	141	141		141	141
K: 3.5-5.0 MEQ/L	4.2	4.1		4.3	4.3
CL: 96-109 MEQ/L	103	105		106	101
CO2: 24-30 MEQ/L	28	28		29	27
SUN: 12-25 MG/DL	8	13		11	12
CREAT: 0.4-1.5 MG/DL	1.0	1.1		0.9	0.9
GLU: 70-115 MG/DL	120	76		82	76
T. BILI: 0.3-1.2 MG/DL	0.7	0.7		0.6	0.6
D. BILI: 0.1-0.4 MG/DL	0.1	0.1		0.0	0.0
CA: 9.0-11.0 MG/DL	8.8	9.2		9.0	9.7
PO4: 3.0-4.5 MG/DL	3.3	2.9		3.1	3.3
URIC A: 4.2-8.8 MG/DL	4.6	4.8		4.3	5.5
T. PROT: 6.0-8.5 G/DL	6.9	6.5		—	6.8
ALB.: 3.2-5.3 G/DL	4.3	4.1		4.1	4.6
AST: 0-35 IU/L	17	12		12	22
ALT: 0-30 IU/L	10	19		8	14
ALK PHOS: 0-95 IU/L	50	48		43	47
CHOL: 151-268 MG/DL	153	157		151	184
LDH: 0-200 IU/L	—	118	136	121	—
CPK: 0-160 U/L (male)	—	74	57	53	—

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	W H U F M L	08	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	21 Jan 86 ddmmmyy	26 Jan 86 ddmmmyy	28 Jan 86 ddmmmyy	31 Jan 86 ddmmmyy	----- ddmmmyy	Date
Hgb	13.9-16.3	15.0	14.7	14.6	15.1		
PCV	41.0-53.0	44.8	43.6	42.5	44.8		
Plt	150-350	161	216	257	337		
RBC	4.50-5.90	4.78	4.61	4.52	4.85		
WBC	4500-11000	6700	5300	6000	7300		
Bands	2-6%	16	5	6	3		
Polys	31-76%	58	49	50	47		
Eos	1-4%	3	4	3	3		
Bas		0	0	0	0		
Lymphs	24-44%	17	32	31	40		
Atyp Lym		0	1	0	1		
Monos	2-11%	6	9	10	6		
Other		0	0	0	0		
Retics	0.5-1.5%	0.3	ND	ND	ND		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	W H L F M L	018	Pyridostigmine
			PROTOCOL
			DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

TEST	NORMAL	Screen	Predrug	Study		Date
		22 Jan 86 ddmmmyy	28 Jan 86 ddmmmyy	31 Jan 86 ddmmmyy	ddmmmyy	ddmmmyy
Color/Sp		clear	yellow	cloudy		
Sp. Gr.		1.022	1.020	1.019		
pH		7.0	6.5	6.0		
Protein		neg	neg	neg		
Ketones		neg	neg	neg		
Occ Bld		neg	neg	neg		
Bili.		neg	neg	neg		
RBC		0	0	0		
WBC		0	0	rare		
Casts		0	0	0		
Epi. Cel		0	0	0		
Crystals		0	0	0		
Bacteria		0	0	0		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
22 Jan 86	✓		
28 Jan 86	✓		
31 Jan 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>W H U</u> F M L	<u>D18</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		— — — dd mmm yy	— — — dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		— (0-2400)	— (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> UNKNOWN
					<input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug
#		— — — dd mmm yy	— — — dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		— (0-2400)	— (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	<input type="checkbox"/> UNKNOWN
					<input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>MEC</u> F M L	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	17 JAN 86	Screening laboratory
—	22 JAN 86	History, Physical Exam
0	27 JAN 86	Admission
2	28 JAN 86	IV
5	31 JAN 86	ORAL

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 019.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent J. Pitty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 22 Jan 86
dd mm yy

Examiner Brent G. Petty, M.D.

Date of birth 12 Apr 63
dd mm yy

BRENT G. PETTY, M.D.
print name

Age 22 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Tobacco Use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>1/2 ppd</u>
Alcohol Use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>6 pack / week</u>
Recreational Drug Use	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Medications past 2 weeks	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Experimental Drug Exposure	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>Pharmacokinetics 8/85</u>
Blood or plasma donor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prior Surgery	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>Umbilical herniorrhaphy age 10</u>
Eye, ear, nose, throat	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Endocrine (diabetes, thyroid)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
C-V (heart murmur, HBP)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pulmonary (cough, asthma)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Hepatitis, gastro-intestinal	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Genito-urinary	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>April 1985</u> <u>GC & PCN</u>
Musculoskeletal	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Neuropsychiatric	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Pesticide/herbicide use	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<u>Exterminators sprayed 9/85</u>
Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> F M L	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 22 Apr 1986
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>36.6</u> C	<u>80</u> /min	<u>16</u> /min	<u>116</u> / <u>78</u>	<u>178.0</u>	<u>61.6</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		
Chest, lungs	✓		
Heart	✓		
Abdomen		✓	<i>Deformed umbilicus</i>
Genitalia	<i>NR</i>		
Rectal	<i>NR</i>		
Extremities	✓		
Skin		✓	<i>Patchy hyperpigmentation on trunk, neck, and arms, possible tinea versicolor. Scar (R) forearm from childhood burn</i>
Neurologic	✓		<i>left handed, left grip > (R)</i>

CHEST X-RAY

Date 22 Apr 1986

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty, M.D.

Brent G. Petty, M.D.
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	019	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

pt's wt 60.8 kg.

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 JAN 86	0917	0947	IV	NA

syringe + pyrid = 42.73

syringe - pyrid = 22.95 ⁴ DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

L.R. NB: This page was created on 22 APR 86. Times for B02-B05 changed.

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	28 JAN 86	0807	0807	B01: *	B47: 11.18
B02	0.08	"	0922	0922	B02: 10.8	
B03	0.16	"	0927	0927	B03: 17.1	
B04, B48	0.25	"	0932	0932	B04: 17.5	B48: 9.08
B05	0.33	"	0937	0937	B05: 18.6	
B06	0.42	"	0942	0942	B06: 14.2	
B07, B49	0.50	"	0947	0947	B07: 24.2	B49: 7.21
B08	0.58	"	0952	0952	B08: 17.6	
B09	0.66	"	0957	0957	B09: 10.1	
B10, B50	0.75	"	1002	1002	B10: 8.42	B50: 7.95
B11	0.83	"	1007	1007	B11: 6.93	
B12	0.92	"	1012	1012	B12: 6.80	
B13, B51	1.0	"	1017	1017	B13: 7.12	B51: 8.07
B14, B52	1.33	"	1037	1037	B14: 5.07	B52: 8.61
B15, B53	1.66	"	1057	1057	B15: 3.16	B53: 9.36
B16, B54	2.0	"	1117	1117	B16: 1.81	B54: 9.70
B17	2.5	"	1147	1147	B17: 6.59	

* Unlabeled and unlabeled ...

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{M}{F} \frac{E}{M} \frac{C}{L}$	019	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 Jun 86	0917	0947	IV	NA

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO]	RBC AChE uM/ml/min
B18, B55	3.0	28 Jun 86	1217	1217	B18: 3.66	B55: 10.38
B19	3.5	"	1247	1247	B19: 3.71	
B20, B56	4.0	"	1317	1317	B20: 1.54	B56: 10.58
B21	5.0	"	1417	1417	B21: *	
B22, B57	6.0	"	1517	1517	B22: *	B57: 10.83
B23	7.0	"	1617	1617	B23: *	
B24	8.0	"	1717	1717	B24: *	
B25	10.0	"	1917	1917	B25: *	
B26	12.0	"	2117	2117	B26: NR	
B27, B58	24.0	29 Jun 86	0917	0910	B27: *	B58: 10.97

* below assay sensitivity N.R. = Not Run

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	M E C F M L	09	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 Jan 86	0917	0947	IV	N/A

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	28 Jan 86	0915	0915	#60	# ND	# OK
	0.8						
	0.16						
	0.25	"	0932	0932	#62		
	0.33						
	0.42						
	0.50	"	0947	0947	#64	# ND	# OK
	0.58						
	0.66						
	0.75	"	1002	1002	#68		
	0.83						
	0.92						
	1.0	"	1017	1017	#70	# ND	
	1.33	"	1037	1037	#70		
	1.66	"	1057	1057	#68		
	2.0	"	1117	1117	#68	# ND	
	2.5						

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	019	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 Aug 86	0917	0947	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>31 Jan 86</u>	<u>0811</u>	<u>0811</u>	<u>PO</u>	<u>N/A</u>

sprunge + pyrido = 7.63020 g
sprunge - pyrido = 5.95638 g

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>NG/ML</u>	RBC ACHe <u>uM/ml/min</u>
B28, B59	0	<u>31 Jan 86</u>	<u>0811</u>	<u>0808</u>	B28: *	B59: 11.17
B29, B60	0.25	"	<u>0826</u>	<u>0826</u>	B29: 4.16	B60: 10.06
B30, B61	0.50	"	<u>0841</u>	<u>0841</u>	B30: 15A	B61: 8.96
B31, B62	0.75	"	<u>0856</u>	<u>0856</u>	B31: 8.17	B62: 8.22
B32, B63	1.0	"	<u>0911</u>	<u>0911</u>	B32: 13.3	B63: 7.71
B33, B64	1.33	"	<u>0931</u>	<u>0931</u>	B33: 11.0	B64: 7.78
B34, B65	1.66	"	<u>0951</u>	<u>0951</u>	B34: 8.45	B65: 8.20
B35, B66	2.0	"	<u>1011</u>	<u>1011</u>	B35: 8.39	B66: 8.42
B36	2.5	"	<u>1041</u>	<u>1041</u>	B36: 6.22	
B37, B67	3.0	"	<u>1111</u>	<u>1111</u>	B37: 5.04	B67: 8.86
B38	3.5	"	<u>1141</u>	<u>1141</u>	B38: 3.74	
B39, B68	4.0	"	<u>1211</u>	<u>1211</u>	B39: 5.38	B68: 9.25
B40	5.0	"	<u>1311</u>	<u>1311</u>	B40: 3.99	
B41, B69	6.0	"	<u>1411</u>	<u>1411</u>	B41: 7.02	B69: 9.80
B42	7.0	"	<u>1511</u>	<u>1511</u>	B42: 2.59	
B43	8.0	"	<u>1611</u>	<u>1611</u>	B43: 1.78	B69A: 10.37
B44	10.0	"	<u>1811</u>	<u>1811</u>	B44: *	B69B: 10.30

* below assay sensitivity 421

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> <u>E</u> <u>C</u> <u>F</u> <u>M</u> <u>L</u>	019	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	31 Aug 86	0811	0811	PO	NA

DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* helms assay sensitivity 422

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	819	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	31 Jan 86	0811	0811	PO	72A

DOSAGE (total) 16 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	31 Jan 86	0811	0808	# 62	# ND	# OK
	0.25	"	0826	0826	# 60		-
	0.50	"	0841	0841	# 58	# ND	# OK
	0.75	"	0856	0856	# 54		
	1.0	"	0911	0911	# 56	# ND	
	1.33	"	0931	0931	# 56		
	1.66	"	0951	0951	# 56		
	2.00	"	1011	1011	# 62	# ND	
	2.5						
	3.0	"	1111	1111	# 60		
	3.5						
	4.0	"	1211	1211	# 70	# ND	
	5.0						
	6.0	"	1411	1411	# 64	# ND	
	7.0						
	8.0						
	10.0						

N.B.: Subject was smoking at 4.0 hours when pulse rate was 70 bpm

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	<u>49</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	<u>17 Jan 86</u> ddmmyy	<u>27 Jan 86</u> ddmmyy	<u>28 Jan 86</u> ddmmyy	<u>29 Jan 86</u> ddmmyy	<u>01 Feb 86</u> ddmmyy
NA: 135-148 MEQ/L	145	140		138	140
K: 3.5-5.0 MEQ/L	4.1	4.5		4.2	3.9
CL: 96-109 MEQ/L	109	104		107	102
CO2: 24-30 MEQ/L	25	28		26	28
SUN: 12-25 MG/DL	—	16		14	17
CREAT: 0.4-1.5 MG/DL	1.0	1.1		1.1	1.1
GLU: 70-115 MG/DL	95	94		75	64
T. BILI: 0.3-1.2 MG/DL	0.6	0.4		0.4	0.7
D. BILI: 0.1-0.4 MG/DL	0.1	0.0		0.1	0.1
CA: 9.0-11.0 MG/DL	9.9	10.5		9.2	10.2
PO4: 3.0-4.5 MG/DL	4.0	4.1		3.1	4.6
URIC A: 4.2-8.8 MG/DL	7.2	8.3		7.5	7.5
T. PROT: 6.0-8.5 G/DL	7.2	7.3		6.3	6.9
ALB.: 3.2-5.3 G/DL	4.5	4.8		4.2	4.5
AST: 0-35 IU/L	19	17		4	13
ALT: 0-30 IU/L	11	5		7	9
ALK PHOS: 0-95 IU/L	50	49		42	—
CHOL: 151-268 MG/DL	178	191		182	192
LDH: 0-200 IU/L	—	99		108	93
CPK: 0-160 U/L (male)	—	136	86	72	59

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E C</u> <u>F M L</u>	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory Johns Hopkins Hospital

		Screen	Predrug	Study	
		17 Jan 86	27 Jan 86	29 Jan 86	31 Jan 86
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy
Hgb	13.9-16.3	16.0	16.9	15.2	16.3
PCV	41.0-53.0	46.7	48.4	44.7	47.7
Plt	150-350	216	211	191	197
RBC	4.50-5.90	5.24	5.51	5.02	5.3
WBC	4500-11000	5100	4900	6500	6200
Bands	2-6%	1	4	5	3
Polys	31-76%	40	48	57	59
Eos	1-4%	3	2	0	2
Bas		0	1	1	0
Lymphs	24-44%	44	34	30	31
Atyp Lym		0	1	1	0
Monos	2-11%	12	10	6	10
Other		0	0	0	0
Retics	0.5-1.5%	—	—	—	0.8

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{M}{F} \frac{E}{M} \frac{C}{L}$	019	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

TEST	NORMAL	Screen	Predrug	Study		
		22 Jan 86	27 Jan 86	29 Jan 86	1 Feb 86	Date
		ddmmyy	ddmmyy	ddmmyy	ddmmyy	ddmmyy
Color/Sp		yellow	clear	clear	—	
Sp. Gr.		1.021	1.017	1.017	1.030	
pH		6.5	5.0	5.0	5.0	
Protein		Trace	Trace	neg	neg	
Ketones		neg	neg	neg	neg	
Occ Bld		neg	neg	neg	neg	
Bili.		neg	neg	neg	neg	
RBC		0	0	0	0	
WBC		0	0	0	0-1	
Casts		0	0	0	0	
Epi. Cel		0	0	0	2	
Crystals		0	0	0	0	
Bacteria		0	0	0	0	

ELECTROCARDIOGRAM

Date	NORMAL	ABNORMAL	Describe abnormalities
ddmmyy	check	check	
22 Jan 86	✓		
29 Jan 86	✓		
01 Feb 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M E 2</u> F M L	<u>019</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		__ __ __ dd mmm yy	__ __ __ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		 _____ (0-2400)	 _____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug
#		__ __ __ dd mmm yy	__ __ __ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		 _____ (0-2400)	 _____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J I R F M L	020	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	23 JAN 86	Screening laboratory
—	24 JAN 86	History, Physical Exam
0	27 JAN 86	Admission
2	28 JAN 86	IV
5	31 JAN 86	PO

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 20.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt G. Petty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J I R</u> F M L	<u>20</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 24 / JAN / 86
dd mm yy

Examiner Brent G. Petty

Date of birth 17 / JAN / 86
dd mm yy

Brent G. Petty
print name

Age 24 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use		✓	1 cpd
Alcohol Use		✓	6 pack + 2-3 mixed drinks / weekend
Recreational Drug Use		✓	M-J 1985
Medications past 2 weeks	✓		
Experimental Drug Exposure	✓		
Blood or plasma donor		✓	last July 1985
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Exterminators in Oct. 1985
Other			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J T R</u> <u>F M L</u>	<u>020</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 24/ JAN 86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.0C</u>	<u>80/min</u>	<u>16/min</u>	<u>108/64</u>	<u>181.0</u>	<u>76.2</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck		✓	slightly asymmetric thyroid ↑ (L) lobe
EENT		✓	Nasal septum deviated to (R), teeth in fair - poor repair
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia			ND
Rectal			ND
Extremities	✓		
Skin		✓	small scar (R) flank ± sl. keloid. formation
Neurologic	✓		

CHEST X-RAY

Date 24/ JAN 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD

Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND	Pyridostigmine
Lietman	J I R F M L	020	PROTOCOL	DAMD 17-85-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 JAN 86	0923	0953	IV	NA

DOSAGE (total) 1.32 mg.**PLASMA CONCENTRATIONS**

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B18, B55	3.0	28 JAN 86	1223	1223	B18: *	B55: 11.75
B19	3.5	"	1253	1253	B19: *	
B20, B56	4.0	"	1323	1323	B20: *	B56: 12.14
B21	5.0	"	1423	1423	B21: *	
B22, B57	6.0	"	1523	1523	B22: *	B57: 12.25
B23	7.0	"	1623	1623	B23: *	
B24	8.0	"	1723	1723	B24: *	
B25	10.0	"	1923	1923	B25: *	
B26	12.0	"	2123	2123	B26: *	
B27, B58	24.0	29 JAN 86	0923	0920	B27: *	B58: 12.55

* below assay sensitivity 433

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J I R F M L	020	Pyridostigmine
			PROTOCOL DAM-17085-C-5133-02

MEDICATION RECORD**STUDY: IV PYRIDOSTIGMINE**

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 JAN 86	0923	0953	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	28 JAN 86	0800	0800	# 64	# ND	# ok
	0.8	"	0828	0828			
	0.16	"	0933	0933			
	0.25	"	0938	0938	# 56		
	0.33	"	0943	0943			
	0.42	"	0948	0948			
	0.50	"	0953	0953	# 60	# ND	# ND
	0.58	"	0958	0958			
	0.66	"	1003	1003			
	0.75	"	1008	1008	# 64		
	0.83	"	1013	1013			
	0.92	"	1018	1018			
	1.0	"	1023	1023	# 60	# ND	
	1.33	"	1043	1043	# 60		
	1.66	"	1103	1103	# 60		
	2.0	"	1123	1123	# 64	# ND	
	2.5	"	1153	1153			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J I R F M L	020	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	28 JAN 86	0923	0953	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	28 JAN 86	1223	1223	# 72		
	3.5	"	1253	1253			
	4.0	"	1323	1323	# 68	# ND	
	5.0	"	1423	1423			
	6.0	"	1523	1523	# 72	# ND	
	7.0	"	1623	1623			
	8.0	"	1723	1723			
	10.0	"	1923	1923			
	12.0	"	2123	2123			
	24.0	29 JAN 86	0923	0920	# 80	# ND	# OK

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J I R</u> <u>F M L</u>	<u>200</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	31 JAN 84	0814	0814	PO	NA

$\text{seizure} + \text{pyridostigmine} = 7.63334$
 $\text{seizure} - \text{pyridostigmine} = 5.95644$

DOSAGE (total) 16 mg**PLASMA CONCENTRATIONS**

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	31 JAN 86	0814	0800	B28: *	B59: 12.66
B29, B60	0.25	"	0829	0829	B29: *	B60: 12.69
B30, B61	0.50	"	0844	0844	B30: 5.62	B61: 11.82
B31, B62	0.75	"	0859	0859	B31: 8.17	B62: 11.24
B32, B63	1.0	"	0914	0914	B32: 6.30	B63: 10.81
B33, B64	1.33	"	0934	0934	B33: 9.86	B64: 10.47
B34, B65	1.66	"	0954	0954	B34: 14.0	B65: 10.03
B35, B66	2.0	"	1014	1014	B35: 13.6	B66: 9.48
B36	2.5	"	1044	1044	B36: 10.3	
B37, B67	3.0	"	1114	1114	B37: 12.1	B67: 8.94
B38	3.5	"	1144	1144	B38: 12.1	
B39, B68	4.0	"	1214	1214	B39: 8.14	B68: 9.73
B40	5.0	"	1314	1314	B40: 5.45	
B41, B69	6.0	"	1414	1414	B41: 4.07	B69: 10.69
B42	7.0	"	1514	1514	B42: 5.90	
B43	8.0	"	1614	1614	B43: 5.50	B69A: 11.73
B44	10.0	"	1814	1814	B44: 4.58	11.49

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J T R</u> <u>F M L</u>	<u>120</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	31 JAN 86	0814	0814	PO	NA

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	J I R F M L	22	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	31 JAN 86	0814	0814	PO	NA

DOSAGE (total) 16mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	31 JAN 86	0814	0805	# 62	# ND	# ok
	0.25	"	0829	0829	# 58		-
	0.50	"	0844	0844	# 56	# ND	# ok
	0.75	"	0859	0859	# 59		
	1.0	"	0914	0914	# 56	# ND	
	1.33	"	0934	0934	# 56		
	1.66	"	0954	0954	# 60		
	2.00	"	1014	1014	# 56	# ND	
	2.5	"	1044	1044			
	3.0	"	1114	1114	# 56		
	3.5	"	1144	1144			
	4.0	"	1214	1214	# 60	# ND	
	5.0	"	1314	1314			
	6.0	"	1414	1414	# 68	# ND	
	7.0	"	1514	1514			
	8.0	"	1614	1614			
	10.0	"	1814	1814			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	J I R F M L	020	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

TEST: NORMAL	Screen	Predrug	Study		
	24 JAN 86 ddmmmyy	27 JAN 86 ddmmmyy	28 JAN 86 ddmmmyy	29 JAN 86 ddmmmyy	01 FEB 86 ddmmmyy
NA: 135-148 MEQ/L	144	141		140	146
K: 3.5-5.0 MEQ/L	4.3	4.1		4.3	4.0
CL: 96-109 MEQ/L	105	108		106	104
CO2: 24-30 MEQ/L	22	19		25	28
SUN: 12-25 MG/DL	21 ¹⁵	14		18	14
CREAT: 0.4-1.5 MG/DL	1.3	1.2		1.1	1.1
GLU: 70-115 MG/DL	76	81		79	65
T. BILI: 0.3-1.2 MG/DL	0.4	0.5		0.6	0.6
D. BILI: 0.1-0.4 MG/DL	0.0	0.0		0.1	0.1
CA: 9.0-11.0 MG/DL	10.3	10.2		9.6	10.2
PO4: 3.0-4.5 MG/DL	5.0	4.3		4.2	4.9
URIC A: 4.2-8.8 MG/DL	4.7	5.3		5.3	5.3
T. PROT: 6.0-8.5 G/DL	7.4	7.3		7.1	7.0
ALB.: 3.2-5.3 G/DL	5.0	5.0		4.7	4.7
AST: 0-35 IU/L	15	15		10	15
ALT: 0-30 IU/L	8	8		9	9
ALK PHOS: 0-95 IU/L	52	52		44	ND
CHOL: 151-268 MG/DL	217	230		229	218
LDH: 0-200 IU/L	ND	ND		128	102
CPK: 0-160 U/L (male)	ND	ND	85	76	80

NB: No labs on 31 JAN 86

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J T R</u> <u>F M L</u>	<u>20</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	<u>24 JAN 86</u> ddmmmyy	<u>27 JAN 86</u> ddmmmyy	<u>29 JAN 86</u> ddmmmyy	<u>01 Feb 86</u> ddmmmyy	<u> </u> ddmmmyy	Date
Hgb	13.9-16.3	14.7	14.7	14.2	14.2		
PCV	41.0-53.0	43.5	43.2	42.2	41.2		
Plt	150-350	264	252	262	258		
RBC	4.50-5.90	4.89	4.84	4.67	4.59		
WBC	4500-11000	5400	6100	4900	5400		
Bands	2-6%	5	5	4	3		
Polys	31-76%	40	27	54	46		
Eos	1-4%	3	1	4	3		
Bas		0	1	0	1		
Lymphs	24-44%	46	36	31	38		
Atyp Lym		1	2	0	0		
Monos	2-11%	5	8	7	9		
Other		0	0	0	0		
Retics	0.5-1.5%	ND	ND	ND	1.6		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J</u> <u>IR</u> F M L	<u>20</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	<u>N.D.</u> ddmmmyy	<u>27 JAN 86</u> ddmmmyy	<u>29 JAN 86</u> ddmmmyy	<u>01 Feb 86</u> ddmmmyy	Date ddmmmyy
Color/Sp			yellow	yellow	ND	
Sp. Gr.			1.019	1.024	1.023	
pH			6.0	6.5	6.0	
Protein			neg	neg	neg	
Ketones			neg	neg	neg	
Occ Bld			neg	neg	neg	
Bili.			neg	neg	neg	
RBC			0	0	0	
WBC			0	0	0-1	
Casts			0	0	0	
Epi. Cel			0	0	0	
Crystals			0	0	0	
Bacteria			0	0	0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
<u>24 JAN 86</u>	✓		
<u>29 JAN 86</u>	✓		
<u>2 Feb 86</u>		✓	<i>developed T wave changes</i>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>J I R</u> <u>F M L</u>	<u>20</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>m</u> <u>-</u> <u>P</u> <u>F</u> <u>M</u> <u>L</u>	<u>021</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmmyy	Procedures
—	27 JAN 86	Screening laboratory
—	30 JAN 86	History, Physical Exam
0	2 FEB 86	Admission
2	3 FEB 86	P.O.
5	6 FEB 86	IV

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 21.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> <u>P</u> <u>F</u> <u>M</u> <u>L</u>	<u>021</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation

30 JAN
01, 30, 86
dd mm yy
16 MAR

Examiner

B. Petty
Brent G. Petty, M.D.
print name

Date of birth

03, 16, 66
dd mm yy

Age

19 yrs

Sex

M

Race

B

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1 ppd
Alcohol Use	✓		
Recreational Drug Use		✓	M-J occasional, last 12/81/85
Medications past 2 weeks	✓		
Experimental Drug Exposure	✓		
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	M - P F M L	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 01/30/86
dd mm yy
30 JAN

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.3</u>	<u>80</u> /min	<u>20</u> /min	<u>124/80</u>	<u>177.0</u>	<u>72.3</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	Left eye sl large @ TM & brain natural over left reflex. White regular lesion @ triller fossa
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia	NP		
Rectal	NO		
Extremities	✓		
Skin		✓	Similar hyperpigmented area on arm from hot grease burn
Neurologic	✓		left handed

CHEST X-RAY

Date 02/ Feb/ 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL	<input type="checkbox"/>	Describe abnormalities:

Examiner

Brent G. Petty
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{matrix} M & - & P \\ F & M & L \end{matrix}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06Feb86	0818	0848	IV	NA

Syringe + syringe = 41.82 g
 Syringe - syringe = 21.77 g

DOSAGE (total)

1.32 mg

PLASMA CONCENTRATIONS

07 Feb 86 Subject's weight = 72.4 kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B01, B47	0	06Feb86	N.A.	0814	B01: *	B47: 11.59
B02	0.08	"	0823	0823	B02: 19.6	
B03	0.16	"	0828	0828	B03: 16.3	
B04, B48	0.25	"	0833	0833	B04: 20.7	B48: 9.63
B05	0.33	"	0838	0838	B05: 21.7	
B06	0.42	"	0843	0843	B06: 19.0	
B07, B49	0.50	"	0848	0848	B07: 22.7	B49: 8.21
B08	0.58	"	0853	0853	B08: 13.7	
B09	0.66	"	0858	0858	B09: 10.5	
B10, B50	0.75	"	0903	0903	B10: 7.54	B50: 8.99
B11	0.83	"	0908	0908	B11: 7.02	
B12	0.92	"	0913	0913	B12: 5.66	
B13, B51	1.0	"	0918	0918	B13: 3.86	B51: 9.70
B14, B52	1.33	"	0938	0938	B14: 5.84	B52: 10.18
B15, B53	1.66	"	0958	0958	B15: 2.41	B53: 10.40
B16, B54	2.0	"	1018	1018	B16: *	B54: 10.84
B17	2.5	"	1048	1048	B17: *	

* below assay sensitivity 447

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06 Feb 86	0818	0848	IV	NA

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

page 2

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B18, B55	3.0	06 Feb 86	1118	1118	B18: *	B55: 10.43
B19	3.5	"	1148	1148	B19: *	
B20, B56	4.0	"	1218	1218	B20: *	B56: 11.12
B21	5.0	"	1318	1318	B21: *	
B22, B57	6.0	"	1418	1418	B22: *	B57: 11.50
B23	7.0	"	1518	1518	B23: *	
B24	8.0	"	1618	1618	B24: *	
B25	10.0	"	1818	1818	B25: *	
B26	12.0	"	2018	2018	B26: *	
B27, B58	24.0	07 Feb 86	0818	0818	B27: *	B58: 11.55

* below assay sensitivity 448

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> <u>P</u> <u>F</u> <u>M</u> <u>L</u>	<u>021</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06 Feb 86	0818	0848	IV	NA

DOSAGE (total) 1.32 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	06 Feb 86	NA	0814	# 68	# ND	# OK
	0.8	"	0823	0823			
	0.16	"	0828	0828			
	0.25	"	0833	0833	# ND		
	0.33	"	0838	0838			
	0.42	"	0843	0843			
	0.50	"	0848	0848	# 68	# ND	# OK
	0.58	"	0853	0853			
	0.66	"	0858	0858			
	0.75	"	0903	0903	# 60		
	0.83	"	0908	0908			
	0.92	"	0913	0913			
	1.0	"	0918	0918	# 64	# ND	
	1.33	"	0938	0938	# 68		
	1.66	"	0958	0958	# 64		
	2.0	"	1018	1018	# 60	# ND	
	2.5	"	1048	1048			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> - <u>P</u> <u>F</u> <u>M</u> <u>L</u>	<u>21</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>5</u>	<u>06Feb86</u>	<u>0818</u>	<u>0848</u>	<u>IV</u>	<u>NA</u>

DOSAGE (total) 1.32 mg**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	<u>06Feb86</u>	<u>1118</u>	<u>1118</u>	<u># 64</u>		
	3.5	<u>"</u>	<u>1148</u>	<u>1148</u>			
	4.0	<u>"</u>	<u>1218</u>	<u>1218</u>	<u># 60</u>	<u># ND</u>	
	5.0	<u>"</u>	<u>1318</u>	<u>1318</u>			
	6.0	<u>"</u>	<u>1418</u>	<u>1418</u>	<u># 64</u>	<u># ND</u>	
	7.0	<u>"</u>	<u>1518</u>	<u>1518</u>			
	8.0	<u>"</u>	<u>1618</u>	<u>1618</u>			
	10.0	<u>"</u>	<u>1818</u>	<u>1818</u>			
	12.0	<u>"</u>	<u>2018</u>	<u>2018</u>			
	24.0	<u>07Feb86</u>	<u>0818</u>	<u>0818</u>	<u># 68</u>	<u># ND</u>	<u># ok</u>

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M} - \frac{L}{L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	03Feb86	0856	0856	PO	NA

syringe + syringe = 7.65638
 syringe - syringe = 5.96912

DOSAGE (total)

16 mg

PLASMA CONCENTRATIONS

Subject's wt: 73.1 kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	03Feb86	0810	0810	B28: *	B59: 11.56
B29, B60	0.25	"	0911	0911	B29: 1.93	B60: 11.66
B30, B61	0.50	"	0926	0926	B30: 5.02	B61: 11.00
B31, B62	0.75	"	0941	0940	B31: 8.58	B62: 10.45
B32, B63	1.0	"	0956	0956	B32: 11.5	B63: 9.69
B33, B64	1.33	"	1016	1016	B33: 9.74	B64: 9.52
B34, B65	1.66	"	1036	1036	B34: 10.1	B65: 9.24
B35, B66	2.0	"	1056	1056	B35: 10.9	B66: 9.02
B36	2.5	"	1126	1126	B36: 5.56	
B37, B67	3.0	"	1156	1156	B37: 7.35	B67: 9.57
B38	3.5	"	1226	1226	B38: 3.76	
B39, B68	4.0	"	1256	1256	B39: 5.70	B68: 9.98
B40	5.0	"	1356	1356	B40: 2.33	
B41, B69	6.0	"	1456	1456	B41: 3.90	B69: 10.83
B42	7.0	"	1556	1556	B42: 3.34	
B43	8.0	"	1656	1656	B43: *	B69A: 11.02
B44	10.0	"	1856	1856	B44: *	11.01

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> F <u>M</u> <u>L</u>	<u>101</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	03Feb84	0856	0856	PO	NA

DOSAGE (total) _____ 6 mg

PLASMA CONCENTRATIONS

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	03 Feb 86	0856	0856	PO	NA

DOSAGE (total) -----

16 mg

PHYSIOLOGIC VARIABLES

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	03 Feb 86	0810	0810	# 74	# ND	# ok
	0.25	"	0911	0911	# 60		-
	0.50	"	0926	0926	# 72	# ND	# ND
	0.75	"	0941	0940	# 72		
	1.0	"	0956	0956	# 64	# ND	
	1.33	"	1016	1016	# 68		
	1.66	"	1036	1036	# 64		
	2.00	"	1056	1056	# 68	# ND	
	2.5	"	1126	1126			
	3.0	"	1156	1156	# 68		
	3.5	"	1226	1226			
	4.0	"	1256	1256	# 72	# ND	
	5.0	"	1356	1356			
	6.0	"	1456	1456	# 72	# ND	
	7.0	"	1556	1556			
	8.0	"	1656	1656			
	10.0	"	1856	1856			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} \frac{P}{M} \frac{P}{L}$	221	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug		Study	
TEST: NORMAL	21 JAN 86 ddmmmyy	02 Feb 86 ddmmmyy	03 Feb 86 ddmmmyy	04 Feb 86 ddmmmyy	06 Feb 86 ddmmmyy
NA:135-148 MEQ/L	141	141	141	139	
K:3.5-5.0 MEQ/L	4.2	4.3		4.6	
CL:96-109 MEQ/L	102	106		106	
CO2:24-30 MEQ/L	28	26		21	
SUN:12-25 MG/DL	11	9		14	
CREAT:0.4-1.5 MG/DL	1.0	1.2		1.1	
GLU:70-115 MG/DL	78	119		99	
T. BILI:0.3-1.2MG/DL	1.1	0.8		0.4	
D. BILI:0.1-0.4MG/DL	0.1	0.1		0.1	
CA:9.0-11.0 MG/DL	9.8	9.8		9.6	
PO4:3.0-4.5 MG/DL	4.6	3.4		3.8	
URIC A:4.2-8.8MG/DL	3.8	4.7		4.9	
T. PROT:6.0-8.5G/DL	7.1	ND		7.1	
ALB.:3.2-5.3 G/DL	4.7	4.6		4.4	
AST:0-35 IU/L	16	19		26	
ALT:0-30 IU/L	10	12		14	
ALK PHOS:0-95 IU/L	44	43		46	
CHOL:151-268 MG/DL	122	120		129 188	
LDH:0-200 IU/L	ND	ND	186	188	176
CPK:0-160 U/L (male)	ND	ND	151	141	170

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M} - \frac{L}{L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug		Study	
TEST: NORMAL	<u>NA</u> ddmmyy	<u>NA</u> ddmmyy	<u>07 Feb 86</u> ddmmyy	<u>ddmmyy</u>	<u>ddmmyy</u> Date
NA: 135-148 MEQ/L			141		
K: 3.5-5.0 MEQ/L			4.5		
CL: 96-109 MEQ/L			106		
CO2: 24-30 MEQ/L			21		
SUN: 12-25 MG/DL			11		
CREAT: 0.4-1.5 MG/DL			1.0		
GLU: 70-115 MG/DL			85		
T. BILI: 0.3-1.2 MG/DL			0.3		
D. BILI: 0.1-0.4 MG/DL			ND		
CA: 9.0-11.0 MG/DL			9.9		
PO4: 3.0-4.5 MG/DL			4.0		
URIC A: 4.2-8.8 MG/DL			4.0		
T. PROT: 6.0-8.5 G/DL			7.3		
ALB.: 3.2-5.3 G/DL			4.7		
AST: 0-35 IU/L			44		
ALT: 0-30 IU/L			36		
ALK PHOS: 0-95 IU/L			45		
CHOL: 151-268 MG/DL			148		
LDH: 0-200 IU/L			133		
CPK: 0-160 U/L (male)			173		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

		Screen		Predrug		Study	
		27 JAN 86	02 Feb 86	04 Feb 86	07 Feb 86	Date	
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Hgb	13.9-16.3	15.5	15.1	ND	15.2		
PCV	41.0-53.0	45.2	43.7	ND	43.5		
Plt	150-350	241	262	ND	268		
RBC	4.50-5.90	5.21	5.02	ND	5.08		
WBC	4500-11000	10500	10700	ND	9200		
Bands	2-6%	10	4	ND	7		
Polys	31-76%	57	68	ND	48		
Eos	1-4%	3	0	ND	0		
Bas		0	0	ND	0		
Lymphs	24-44%	25	22	ND	39		
Atyp Lym		2	1	ND	0		
Monos	2-11%	3	5	ND	6		
Other		0	0	ND	0		
Retics	0.5-1.5%	ND	ND	ND	1.0		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{M}{F} - \frac{P}{M L}$	021	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

Johns Hopkins University
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	<u>ND</u> ddmmyy	<u>02Feb86</u> ddmmyy	<u>04Feb86</u> ddmmyy	<u>07Feb86</u> ddmmyy	_____ Date
Color/Sp			clear	ND	yellow	
Sp. Gr.			1.020		1.019	
pH			6.0		6.0	
Protein			neg		neg	
Ketones			neg		neg	
Occ Bld			neg		neg	
Bili.			neg		neg	
RBC			0		0	
WBC			0		0	
Casts			0		0	
Epi. Cel			0		0	
Crystals			0		0	
Bacteria			0		0	

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
02Feb86	✓		
04Feb86	✓		
07Feb86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>M</u> - <u>P</u> <u>F</u> <u>M</u> <u>L</u>	<u>021</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		____ _ dd mmm yy	____ _ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		____ _ dd mmm yy	____ _ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>L</u> F <u>-</u> M <u>-</u> L <u>W</u>	<u>022</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	17 JAN 86	Screening laboratory
—	30 JAN 86	History, Physical Exam
0	2 FEB 86	Admission
2	03 FEB 86	P.O.
5	06 FEB 86	IV

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 022.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24/01/86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	L - W F M L	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

30 JAN 30
21 OCT 86
MEDICAL HISTORY

Date of evaluation

Examiner

Date of birth

Age

Sex

Race

dd mmm yy

01 Feb

dd mmm yy

23 yrs

M

B

Brent G. Petty
Brent G. Petty
print name

No Yes Comments

Allergy	✓		
Tobacco Use		✓	1 pack
Alcohol Use		✓	2 drinks on weekends
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Cyfloroxone, tobram
Blood or plasma donor	✓		
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary	✓		
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	Used insecticide ~ 3 weeks ago
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>L</u> - <u>W</u> <u>F</u> <u>M</u> <u>L</u>	<u>022</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

30 JAN 86
PHYSICAL EXAMINATION

Date 31-30-86
for dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>36.0</u> C	<u>84</u> min	<u>20</u> /min	<u>118/72</u>	<u>177</u>	<u>70</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT		✓	<u>Few lymphoid follicles anterior pharynx</u>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		<u>ND</u>	
Rectal		<u>ND</u>	
Extremities	✓		
Skin		✓	<u>Scar (L) index finger from knife laceration, vertical scar L&R from bike accident, bilateral volar wrist</u>
Neurologic	✓		

CHEST X-RAYDate 30/ JAN/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{2}{F} - \frac{W}{M L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06Feb86	0825	0855	IV	NA

Syringe + pyrido = 41.41 g
 Syringe - pyrido = 21.58 g

DOSAGE (total) 1.32 mg.**PLASMA CONCENTRATIONS**

Subject's wt. = 69.0

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	06Feb86	0810	0810	B01: *	B47: 15.48
B02	0.08	"	0830	0830	B02: 7.80	
B03	0.16	"	0835	0835	B03: 4.9	
B04, B48	0.25	"	0840	0840	B04: 22.4	B48: 12.21
B05	0.33	"	0845	0845	B05: 21.8	
B06	0.42	"	0850	0850	B06: 24.8	
B07, B49	0.50	"	0855	0855	B07: 20.6	B49: 10.91
B08	0.58	"	0900	0900	B08: 11.6	
B09	0.66	"	0905	0905	B09: 11.3	
B10, B50	0.75	"	0910	0910	B10: 8.55	B50: 11.95
B11	0.83	"	0915	0915	B11: 6.59	
B12	0.92	"	0920	0920	B12: 4.80	
B13, B51	1.0	"	0925	0925	B13: 6.36	B51: 12.64
B14, B52	1.33	"	0945	0945	B14: 4.09	B52: 13.29
B15, B53	1.66	"	1005	1005	B15: 3.66	B53: 13.97
B16, B54	2.0	"	1025	1025	B16: 1.75	B54: 14.11
B17	2.5	"	1055	1055	B17: 2.76	

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} \quad \frac{-}{M} \quad \frac{W}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06Feb88	0825	0855	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 464

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{L}{F} \frac{-}{M} \frac{W}{L}$	022	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06 Feb 86	0825	0855	IV	NR

DOSAGE (total) 1.32 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	06 Feb 86	0800	0800	# 68	# ND	# OK
	0.8	"	0830	0830			
	0.16	"	0835	0835			
	0.25	"	0840	0840	# 60		
	0.33	"	0845	0845			
	0.42	"	0850	0850			
	0.50	"	0855	0855	# 64	# ND	# ND
	0.58	"	0900	0900			
	0.66	"	0905	0905			
	0.75	"	0910	0910	# 64		
	0.83	"	0915	0915			
	0.92	"	0920	0920			
	1.0	"	0925	0925	# 60	# ND	
	1.33	"	0945	0945	# 68		
	1.66	"	1005	1005	# 64		
	2.0	"	1025	1025	# 64	# ND	
	2.5	"	1055	1055			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} = \frac{M}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	06 Feb 86	0825	0855	IV	NA

DOSAGE (total)

1.32 mg.**PHYSIOLOGIC VARIABLES**

page 2

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	3.0	06 Feb 86	1125	1125	# 60		
	3.5	"	1155	1155			
	4.0	"	1225	1225	# ND	# ND	
	5.0	"	1325	1325			
	6.0	"	1425	1425	# 60	# ND	
	7.0	"	1525	1525			
	8.0	"	1625	1625			
	10.0	"	1825	1825			
	12.0	"	2025	2025			
	24.0	07 Feb 86	0825	0825	# 64	# ND	# OK

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} - \frac{M}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	03 Feb 86	0859	0859	PO	NA

Syringe + pyridos. = 7.65638

Syringe - pyridos. = 5.97471

DOSAGE (total)

16 mg

PLASMA CONCENTRATIONS

Subject's weight = 70.7 kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B28, B59	0	03 Feb 86	0820	0820	B28: *	B59: 15.32
B29, B60	0.25	"	0914	0916	B29: 2.81	B60: 14.75
B30, B61	0.50	"	0929	0929	B30: 6.13	B61: 13.56
B31, B62	0.75	"	0944	0944	B31: 14.1	B62: 12.53
B32, B63	1.0	"	0959	0959	B32: 11.4	B63: 11.26
B33, B64	1.33	"	1019	1019	B33: 9.23	B64: 11.27
B34, B65	1.66	"	1039	1039	B34: 10.1	B65: 11.76
B35, B66	2.0	"	1059	1059	B35: 7.57	B66: 11.47
B36	2.5	"	1129	1129	B36: 8.17	
B37, B67	3.0	"	1159	1159	B37: 8.17	B67: 11.19
B38	3.5	"	1229	1229	B38: 7.67	
B39, B68	4.0	"	1259	1259	B39: 5.91	B68: 11.94
B40	5.0	"	1359	1359	B40: 4.77	
B41, B69	6.0	"	1459	1459	B41: 3.56	B69: 13.83
B42	7.0	"	1559	1559	B42: *	
B43	8.0	"	1659	1659	B43: 1.93	B69A: 14.33
B44	10.0	"	1859	1859	B44: *	14.71

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>L</u> F <u>M</u> <u>L</u>	<u>022</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
2	03 Feb 86	0859	0859	PO	NA

DOSAGE (total) 16mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} \frac{-}{M} \frac{-}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	03 Feb 88	0859	0859	PO	NA

DOSAGE (total) 16 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	03 Feb 88	0820	0820	# 70	# ND	# OK
	0.25	"	0914	0916	# 76		-
	0.50	"	0929	0929	# 60	# ND	# ND
	0.75	"	0944	0944	# 56		
	1.0	"	0959	0959	# 60	# ND	
	1.33	"	1019	1019	# 64		
	1.66	"	1039	1039	# 60		
	2.00	"	1059	1059	# 52	# ND	
	2.5	"	1129	1129			
	3.0	"	1159	1159	# 60		
	3.5	"	1229	1229			
	4.0	"	1259	1259	# 64	# ND	
	5.0	"	1359	1359			
	6.0	"	1459	1459	# 60	# ND	
	7.0	"	1559	1559			
	8.0	"	1659	1659			
	10.0	"	1859	¹⁸⁵⁹ 1860			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} - \frac{W}{M} - \frac{L}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hsptl.

Screen Predrug

Study

TEST: NORMAL	17 JAN 86 ddmmmyy	02 Feb 86 ddmmmyy	03 Feb 86 ddmmmyy	04 Feb 86 ddmmmyy	06 Feb 86 ddmmmyy	Date
NA: 135-148 MEQ/L	145	143		139		
K: 3.5-5.0 MEQ/L	4.6	4.1		4.2		
CL: 96-109 MEQ/L	110	109		105		
CO2: 24-30 MEQ/L	24	28		22		
SUN: 12-25 MG/DL	11	16		12		
CREAT: 0.4-1.5 MG/DL	1.1	1.1		1.0		
GLU: 70-115 MG/DL	40	117		156		
T. BILI: 0.3-1.2 MG/DL	0.6	0.9		1.0		
D. BILI: 0.1-0.4 MG/DL	ND	0.1		0.1		
CA: 9.0-11.0 MG/DL	9.6	9.5		9.2		
PO4: 3.0-4.5 MG/DL	3.6	ND		3.6		
URIC A: 4.2-8.8 MG/DL	5.3	5.8		5.0		
T. PROT: 6.0-8.5 G/DL	7.0	6.8		6.4		
ALB.: 3.2-5.3 G/DL	5.1	4.7		4.4		
AST: 0-35 IU/L	11	24		20		
ALT: 0-30 IU/L	3	3		11		
ALK PHOS: 0-95 IU/L	40	49		41		
CHOL: 151-268 MG/DL	207	180		184		
LDH: 0-200 IU/L	ND	ND	128	104	119	
CPK: 0-160 U/L (male)	ND	ND	373	258	207	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} - \frac{W}{M} \frac{L}{L}$	22	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST: NORMAL	<u>NA</u> ddmmmyy	<u>NA</u> ddmmmyy	<u>07Feb84</u> ddmmmyy	ddmmmyy	ddmmmyy	Date
NA: 135-148 MEQ/L			140			
K: 3.5-5.0 MEQ/L			4.1			
CL: 96-109 MEQ/L			104			
CO2: 24-30 MEQ/L			25			
SUN: 12-25 MG/DL			13			
CREAT: 0.4-1.5 MG/DL			1.0			
GLU: 70-115 MG/DL			83			
T. BILI: 0.3-1.2 MG/DL			1.1			
D. BILI: 0.1-0.4 MG/DL			ND			
CA: 9.0-11.0 MG/DL			9.4			
PO4: 3.0-4.5 MG/DL			4.2			
URIC A: 4.2-8.8 MG/DL			5.2			
T. PROT: 6.0-8.5 G/DL			6.8			
ALB.: 3.2-5.3 G/DL			4.8			
AST: 0-35 IU/L			33			
ALT: 0-30 IU/L			18			
ALK PHOS: 0-95 IU/L			41			
CHOL: 151-268 MG/DL			187			
LDH: 0-200 IU/L			104			
CPK: 0-160 U/L (male)			210			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{L}{F} - \frac{M}{L} - \frac{W}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES
Laboratory

Johannes Hopkins Hospital

		Screen		Predrug		Study	
		17 JAN 86	02 Feb 86	04 Feb 86	07 Feb 86	Date	
TEST	NORMAL	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	ddmmmyy	
Hgb	13.9-16.3	14.9	13.8	13.9	13.7		
PCV	41.0-53.0	43.5	40.0	40.8	39.5		
Plt	150-350	220	225	205	218		
RBC	4.50-5.90	4.98	4.64	4.69	4.48		
WBC	4500-11000	4800	4800	4100	5900		
Bands	2-6%	5	4	1	12		
Polys	31-76%	53	48	41	59		
Eos	1-4%	1	3	2	0		
Bas		0	0	0	0		
Lymphs	24-44%	35	33	46	25		
Atyp Lym		0	3	1	0		
Monos	2-11%	6	9	9	4		
Other		0	0	0	0		
Retics	0.5-1.5%	ND	ND	0.4	0.7		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{2}{F} - \frac{W}{M} - \frac{L}{L}$	022	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*Johns Hopkins University
Clinical Pharmacology*

TEST	NORMAL	Screen		Predrug		Study		Date
		<u>N.D.</u> ddmmyy	<u>02 Feb 86</u> ddmmyy	<u>04 Feb 86</u> ddmmyy	<u>07 Feb 86</u> ddmmyy	<u>07 Feb 86</u> ddmmyy	<u>07 Feb 86</u> ddmmyy	
Color/Ap			clear	N.D.	milky			
Sp. Gr.			1.019		1.020			
pH			5.0		5.0			
Protein			neg		(trace) neg			
Ketones			neg		neg			
Occ Bld			neg		neg			
Bili.			neg		neg			
RBC			0		0			
WBC			0		0			
Casts			0		0			
Epi. Cel			0		0			
Crystals			0		0			
Bacteria			0		0			

ELECTROCARDIOGRAM

Date ddmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
30 JAN 86	✓		
04 Feb 86	✓		
07 Feb 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>L</u> F <u>C</u> M <u>W</u> L	<u>02</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT	ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#	dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
	(0-2400)	(0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
			<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug
#	dd mm yy	dd mm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
	(0-2400)	(0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB. <input type="checkbox"/> POSS.	<input type="checkbox"/> Treatment
			<input type="checkbox"/> Sev	<input type="checkbox"/> DEF. NOT <input type="checkbox"/> UNKNOWN	<input type="checkbox"/> Stop test drug

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> F <u>C</u> M <u>M</u> L	<u>023</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	30 JAN 86	Screening laboratory
—	06 FEB 86	History, Physical Exam
0	09 FEB 86	Admission
2	10 FEB 86	I.V.
5	13 FEB 86	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 023.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Burt Willey M.D.
Investigator's signature

24 Oct 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D C M</u> <u>F M L</u>	<u>023</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 06 Feb 02, 06, 86 24 Examiner Brent G. Petty MD
 dd mmm yy
 Date of birth 17 JUN 65 24
 dd mmm yy
 Age 20 yrs
 Sex M
 Race B

Brent G. Petty
print name

	No	Yes	Comments
Allergy		✓	Tomatoe → hives; PCN → hives
Tobacco Use		✓	1/2 pack
Alcohol Use	✓		
Recreational Drug Use	✓		
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	Pharmaceuticals, last 1983
Blood or plasma donor		✓	last 2 months ago
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	GC ~10 years ago, Rx'd c injection
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use		✓	last exterminator's visit ~ 7 yrs ago no pets
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{M}{L}$	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 06/Feb/86
dd mm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>37.5</u> C	<u>72</u> min	<u>20</u> /min	<u>110/70</u>	<u>173.0</u>	<u>83.0</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		<i>Few lymphoid excreta posterior pharynx</i>
Chest, lungs	✓		
Heart	✓		<i>I-II/4 systolic flow (w), diastolic S₂</i>
Abdomen	✓		
Genitalia	ND		
Rectal	ND		
Extremities	✓		<i>mill scarring antecubital fossae from blood/plasma donations</i>
Skin		✓	<i>Tinea versicolor (Darm, low back, cheeks, low chest)</i>
Neurologic	✓		<i>Sar @ forearm, wrist</i>

CHEST X-RAY

Date 06/Feb/86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brent G. Petty MD
Brent G. Petty
 print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D C M</u> <u>F M L</u>	<u>023</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
<u>2</u>	<u>10 Feb 86</u>	<u>0842</u>	<u>0912</u>	<u>IV</u>	<u>NA</u>

Syringe + pyrido = 43.15 g
 syringe - pyrido = 23.13 g

DOSAGE (total) 1.32 mg

pt. wt = 83.3 kg } recorded for this
 pt. wt = 84.5 kg } data in separate
 places in source document

PLASMA CONCENTRATIONS

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] <u>NG/ML</u>	RBC ACHe <u>uM/ml/min</u>
B01, B47	0	<u>10 Feb 86</u>	<u>N.A.</u>	<u>0807</u>	<u>B01: *</u>	<u>B47: 13.34</u>
B02	0.08	"	<u>0847</u>	<u>0847</u>	<u>B02: 12.3</u>	
B03	0.16	"	<u>0852</u>	<u>0852</u>	<u>B03: 8.39</u>	
B04, B48	0.25	"	<u>0857</u>	<u>0857</u>	<u>B04: 16.7</u>	<u>B48: 11.38</u>
B05	0.33	"	<u>0902</u>	<u>0902</u>	<u>B05: 22.6</u>	
B06	0.42	"	<u>0907</u>	<u>0907</u>	<u>B06: 14.9</u>	
B07, B49	0.50	"	<u>0912</u>	<u>0912</u>	<u>B07: 20.5</u>	<u>B49: 9.45</u>
B08	0.58	"	<u>0917</u>	<u>0917</u>	<u>B08: 12.7</u>	
B09	0.66	"	<u>0922</u>	<u>0922</u>	<u>B09: 11.0</u>	
B10, B50	0.75	"	<u>0927</u>	<u>0927</u>	<u>B10: 14.8</u>	<u>B50: 9.71</u>
B11	0.83	"	<u>0932</u>	<u>0932</u>	<u>B11: 9.26</u>	
B12	0.92	"	<u>0937</u>	<u>0937</u>	<u>B12: 7.74</u>	
B13, B51	1.0	"	<u>0942</u>	<u>0942</u>	<u>B13: 3.86</u>	<u>B51: 10.82</u>
B14, B52	1.33	"	<u>1002</u>	<u>1002</u>	<u>B14: 4.24</u>	<u>B52: 11.08</u>
B15, B53	1.66	"	<u>1022</u>	<u>1022</u>	<u>B15: 3.80</u>	<u>B53: 11.32</u>
B16, B54	2.0	"	<u>1042</u>	<u>1042</u>	<u>B16: *</u>	<u>B54: 11.96</u>
B17	2.5	"	<u>1112</u>	<u>1112</u>	<u>B17: 2.92</u>	

* below assay sensitivity 479

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>C</u> <u>M</u> <u>F</u> <u>M</u> <u>L</u>	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u> -----

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10Feb86	0842	0912	IV	NA

DOSAGE (total) 1.32 mg

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity 480 NR := not run

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>C</u> <u>M</u> <u>F</u> <u>M</u> <u>L</u>	<u>023</u>	PROTOCOL <u>DAMD-17085-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10Feb86	0842	0912	IV	NA

DOSAGE (total) 1.32 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	10Feb86	NA	0837	#54	#ND	#ok
	0.8	"	0847	0847			
	0.16	"	0852	0852			
	0.25	"	0857	0857	#60		
	0.33	"	0902	0902			
	0.42	"	0907	0907			
	0.50	"	0912	0912	#64	#ND	#ok
	0.58	"	0917	0917			
	0.66	"	0922	0922			
	0.75	"	0927	0927	#60		
	0.83	"	0932	0932			
	0.92	"	0937	0937			
	1.0	"	0942	0942	#60	#ND	
	1.33	"	1002	1002	#64		
	1.66	"	1022	1022	#60		
	2.0	"	1042	1042	#64	#ND	
	2.5	"	1112	1112			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{m}{L}$	23	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10Feb86	0842	0912	IV	NA

DOSAGE (total)

1.32 mg

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{m}{L}$	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	13Feb86	0858	0858	PO	NA

$\text{Syringe} + \text{pyridos} = 7.689778$
 $\text{Syringe} - \text{pyridos} = 5.983118$

PLASMA CONCENTRATIONS

pts weight = 82.0 kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/mL	RBC AChE uM/ml/min
B28, B59	0	13Feb86	NA	0846	B28: *	B59: 13.34
B29, B60	0.25	"	0913	0913	B29: 4.80	B60: 12.87
B30, B61	0.50	"	0928	0928	B30: 7.77	B61: 11.83
B31, B62	0.75	"	0943	0943	B31: 10.9	B62: 11.36
B32, B63	1.0	"	0958	0958	B32: 14.0	B63: 10.60
B33, B64	1.33	"	1018	1018	B33: 16.1	B64: 10.14
B34, B65	1.66	"	1038	1038	B34: 15.3	B65: 9.88
B35, B66	2.0	"	1058	1058	B35: 13.9	B66: 9.94
B36	2.5	"	1128	1128	B36: 13.4	
B37, B67	3.0	"	1158	1158	B37: 12.3	B67: 9.77
B38	3.5	"	1228	1228	B38: 13.1	
B39, B68	4.0	"	1258	1258	B39: 8.57	B68: 10.22
B40	5.0	"	1358	1358	B40: 7.46	
B41, B69	6.0	"	1458	1458	B41: 4.89	B69: 11.32
B42	7.0	"	1558	1558	B42: 4.60	
B43	8.0	"	1658	1658	B43: 5.29	B69A: 11.61
B44	10.0	"	1858	1858	B44: 1.69	12.29

* below assay sensitivity 483

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D</u> <u>C</u> <u>M</u> <u>F</u> <u>M</u> <u>L</u>	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
5	13 Feb 86	0858	0858	PO	NA

DOSAGE (total)

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{M}{L}$	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	13 Feb 86	0858	0858	PO	NA

DOSAGE (total) 16 mg**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	13 JAN 86	NA	0849	# 60	# ND	# ok
	0.25	"	0913	0913	# 60		-
	0.50	"	0928	0928	# 64	# ND	# ok
	0.75	"	0943	0943	# 68		
	1.0	"	0958	0958	# 64	# ND	
	1.33	"	1018	1018	# 60		
	1.66	"	1038	1038	# 64		
	2.00	"	1058	1058	# 60	# ND	
	2.5	"	1128	1128			
	3.0	"	1158	1158	# 60		
	3.5	"	1228	1228			
	4.0	"	1258	1258	# ND	# ND	
	5.0	"	1358	1358			
	6.0	"	1458	1458	# ND	# ND	
	7.0	"	1558	1558			
	8.0	"	1658	1658			
	10.0	"	1858	1858			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{m}{L}$	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES

Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	30 JAN 86 ddmmmyy	N.D. ddmmmyy	11 Feb 86 ddmmmyy	14 Feb 86 ddmmmyy	Date ddmmmyy
NA: 135-148 MEQ/L	146		141	139	
K: 3.5-5.0 MEQ/L	4.3		4.3	4.2	
CL: 96-109 MEQ/L	107		106	103	
CO2: 24-30 MEQ/L	23		24	25	
SUN: 12-25 MG/DL	15		16	12	
CREAT: 0.4-1.5 MG/DL	1.1		1.0	1.1	
GLU: 70-115 MG/DL	61		89	109	
T. BILI: 0.3-1.2 MG/DL	0.8		1.3	0.6	
D. BILI: 0.1-0.4 MG/DL	0.0		0.1	ND	
CA: 9.0-11.0 MG/DL	10.1		9.7	10.0	
PO4: 3.0-4.5 MG/DL	4.5		3.7	2.9	
URIC A: 4.2-8.8 MG/DL	4.2 ^{7.4}		6.8	7.0	
T. PROT: 6.0-8.5 G/DL	7.6		7.3	7.5	
ALB.: 3.2-5.3 G/DL	4.7		4.7	4.8	
AST: 0-35 IU/L	16		8	16	
ALT: 0-30 IU/L	22		9	11	
ALK PHOS: 0-95 IU/L	59		60	51	
CHOL: 151-268 MG/DL	ND		ND	156	
LDH: 0-200 IU/L	184		121	84	
CPK: 0-160 U/L (male)	ND	✓	76	82	

N.B. CPK + LDH not done on days of dosing

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{D}{F} \frac{C}{M} \frac{M}{L}$	023	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	<u>30 JAN 86</u> ddmmmyy	<u>N.D.</u> ddmmmyy	<u>11 FEB 86</u> ddmmmyy	<u>14 FEB 86</u> ddmmmyy	Date ddmmmyy
Hgb	13.9-16.3	15.2		15.1	15.1	
PCV	41.0-53.0	45.7		45.4	44.8	
Plt	150-350	162		193	176	
RBC	4.50-5.90	4.95		4.93	4.87	
WBC	4500-11000	8200		7600	7300	
Bands	2-6%	7		6	8	
Polys	31-76%	49		50	59	
Eos	1-4%	0		3	0	
Bas		0		0	0	
Lymphs	24-44%	33		31	24	
Atyp Lym		2		2	0	
Monos	2-11%	9		8	9	
Other		0		0	0	
Retics	0.5-1.5%	ND	✓	1.5	1.4	

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{D}{F} \frac{C}{M} \frac{M}{L}$	023	Pyridostigmine
			PROTOCOL DAMD 17-85-C-5133-02

URINALYSIS VALUES

Laboratory

University of Illinois at Chicago
Johns Hopkins Hospital
Clinical Pharmacology

Screen Predrug

Study

TEST	NORMAL	06 Feb 86 ddmmmyy	N. D. L. ddmmmyy	11 Feb 86 ddmmmyy	14 Feb 86 ddmmmyy	----- ddmmmyy	Date
Color/Sp		yellow		N. D.	yellow		
Sp. Gr.		1.020			1.029		
pH		6.0			6.0		
Protein		neg			(trace) neg		
Ketones		neg			neg		
Occ Bld		neg			neg		
Bili.		neg			neg		
RBC		0			0		
WBC		0			0		
Casts		0			0		
Epi. Cel		0			0		
Crystals		0			0		
Bacteria		0	✓	✓	0		

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
06 Feb 86	✓		
11 Feb 86	✓		
14 Feb 86	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>D C M</u> <u>F M L</u>	<u>023</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R m B</u> <u>F M L</u>	<u>024</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

PROTOCOL

Study Day	Date ddmmyy	Procedures
—	03 FEB 86	Screening laboratory
—	06 FEB 86	History, Physical Exam
0	09 FEB 86	Admission
2	10 FEB 86	I.V.
5	13 FEB 86	P.O.

I certify that:

- 1) I have carefully examined all entries on the data collection forms, consisting of 15 pages, for subject # 24.
- 2) All information entered onto the data collection forms for this subject, to the best of my knowledge, is correct.

Brent G. Petty M.D.
Investigator's signature

24, Oct, 86
dd/mm/yy

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R M B</u> <u>F M L</u>	<u>024</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICAL HISTORY

Date of evaluation 06 Feb 86
dd mm yy

Examiner Brent G. Petty MD

Date of birth 24 Feb 53
dd mm yy

Brent G. Petty
print name

Age 32 yrs

Sex M

Race B

	No	Yes	Comments
Allergy	✓		
Tobacco Use	✓		
Alcohol Use		✓	<u>Rarely</u>
Recreational Drug Use		✓	<u>Last used cocaine, 1 1/2 yrs ago</u>
Medications past 2 weeks	✓		
Experimental Drug Exposure		✓	<u>Phenylbutazone ~ 1 yr ago</u>
Blood or plasma donor		✓	<u>Last 1978</u>
Prior Surgery	✓		
Eye, ear, nose, throat	✓		
Endocrine (diabetes, thyroid)	✓		
C-V (heart murmur, HBP)	✓		
Pulmonary (cough, asthma)	✓		
Hepatitis, gastro-intestinal	✓		
Genito-urinary		✓	<u>GC 1977, 14 d PCN</u>
Musculoskeletal	✓		
Neuropsychiatric	✓		
Pesticide/herbicide use	✓		<u>No pets, no insecticides</u>
Other	✓		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R M B</u> <u>F M L</u>	<u>024</u>	PROTOCOL <u>DMD 17-85-C-5133-02</u>

PHYSICAL EXAMINATION

Date 06 Feb 86
dd mmm yy

Temperature	Pulse	Respir	Blood Pressure	Height (cm)	Wt. (kg)
<u>ND</u> C	<u>ND</u> /min	<u>ND</u> /min	<u>ND</u>	<u>ND</u>	<u>ND</u>

GENERAL EXAMINATION:			
(check)	Nor.	Abn.	Provide details of abnormalities
Head/Neck	✓		
EENT	✓		<i>Slightly red tonsillar pillars, few lymphoid accumulations posterior pharynx</i>
Chest, lungs	✓		
Heart	✓		
Abdomen	✓		
Genitalia		<i>ND</i>	
Rectal		<i>ND</i>	
Extremities	✓		
Skin		✓	<i>Modest acne on back, chest, face, buttocks (R) arm - spots, hyperpigmentation. Con (D) scars, buttocks (R) medial thigh → buttocks</i>
Neurologic	✓		<i>left handed</i>

CHEST X-RAY

Date 06 FEB 86

NORMAL	<input checked="" type="checkbox"/>	ABNORMAL		Describe abnormalities:

Examiner

Brant G. Petty (M)
Brant G. Petty
print name

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\begin{smallmatrix} R & M & B \\ F & M & L \end{smallmatrix}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10 Feb 86	0846	0916	IV	NA

Syringe + pyrido = ~~43.16~~ 43.16 g

Syringe - pyrido = 23.04 g

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

pt's weight = 68.0 Kg

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC ACHe uM/ml/min
B01, B47	0	10 Feb 86	NA	0810	B01:*	B47: 10.51
B02	0.08	"	0851	0855	B02: 9.91	
B03	0.16	"	0856	0856	B03: 11.2	
B04, B48	0.25	"	0901	0901	B04: 13.0	B48: 9.02
B05	0.33	"	0906	0906	B05: 19.2	
B06	0.42	"	0911	0911	B06: 22.3	
B07, B49	0.50	"	0916	0916	B07: 20.8	B49: 7.29
B08	0.58	"	0921	0921	B08: 17.0	
B09	0.66	"	0926	0926	B09: 12.4	
B10, B50	0.75	"	0931	0931	B10: 9.04	B50: 8.07
B11	0.83	"	0936	0936	B11: 6.98	
B12	0.92	"	0941	0941	B12: 6.77	
B13, B51	1.0	"	0946	0946	B13: 5.37	B51: 8.51
B14, B52	1.33	"	1006	1006	B14: 3.19	B52: 8.82
B15, B53	1.66	"	1026	1026	B15: 3.77	B53: 9.30
B16, B54	2.0	"	1046	1046	B16: 4.40	B54: 9.22
B17	2.5	"	1116	1116	B17: 4.64	

* below assay sensitivity 494

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> <u>m</u> <u>B</u> <u>F</u> <u>M</u> <u>L</u>	24	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmmyy	Start drug admin- istration (0-2400)	End drug admin- istration (0-2400)	Route	Bottle I.D. #
2	10Feb84	0846	0916	IV	NA

DOSAGE (total) 1.32 mg.

PLASMA CONCENTRATIONS

page 2

[illegible]

* below assay sensitivity

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND
Lietman	$\frac{R}{F} \frac{M}{M} \frac{B}{L}$	024	Pyridostigmine
			PROTOCOL DAMD-17085-C-5133-02

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10 Feb 86	0846	0916	IV	NA

DOSAGE (total) 1.32 mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	10 Feb 86	NA	0835	# 72	# ND	# ok
	0.8	"	0851	0851			
	0.16	"	0856	0856			
	0.25	"	0901	0908	# 78		
	0.33	"	0906	0906			
	0.42	"	0911	0911			
	0.50	"	0916	0916	# 72	# ND	# ok
	0.58	"	0921	0921			
	0.66	"	0926	0926			
	0.75	"	0931	0931	# 86		
	0.83	"	0936	0936			
	0.92	"	0941	0941			
	1.0	"	0946	0946	# 80	# ND	
	1.33	"	1006	1006	# 80		
	1.66	"	1026	1026	# 80		
	2.0	"	1046	1046	# 80	# ND	
	2.5	"	1116	1116			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{M}{M} \frac{B}{L}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: IV PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
2	10/5/86	0846	0916	IV	NA

DOSAGE (total) 1.32 mg.

PHYSIOLOGIC VARIABLES

page 2

[illegible]

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{M}{M} \frac{B}{L}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	13Feb86	0903	0903	PO	

Syringe + syringe = 7.63559g
 syringe - syringe = 5.96846g
 DOSAGE (total) 16 mg.

PLASMA CONCENTRATIONS

14 Feb 86 pt's wt = 68.0

Sample No.	Schedule Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	[PYRIDO] NG/ML	RBC AChE uM/ml/min
B28, B59	0	13Feb86	NA	0849	B28: *	B59: 10.60
B29, B60	0.25	"	0918	0918	B29: 2.00	B60: 10.67
B30, B61	0.50	"	0933	0933	B30: 10.6	B61: 9.02
B31, B62	0.75	"	0948	0948	B31: 10.9	B62: 8.75
B32, B63	1.0	"	1003	1003	B32: 11.6	B63: 7.94
B33, B64	1.33	"	1023	1023	B33: 10.0	B64: 7.95
B34, B65	1.66	"	1043	1043	B34: 13.0	B65: 7.46
B35, B66	2.0	"	1103	1103	B35: 10.6	B66: 7.28
B36	2.5	"	1133	1133	B36: 9.38	
B37, B67	3.0	"	1203	1203	B37: 9.98	B67: 7.81
B38	3.5	"	1233	1233	B38: 9.04	
B39, B68	4.0	"	1303	1303	B39: 9.45	B68: 8.33
B40	5.0	"	1403	1403	B40: 4.62	
B41, B69	6.0	"	1503	1503	B41: 3.41	B69: 9.31
B42	7.0	"	1603	1603	B42: 2.63	
B43	8.0	"	1703	1703	B43: 2.14	B69A: 9.73
B44	10.0	"	1903	1903	B44: 1.84	9.43

* below assay sensitivity 498

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{M}{M} \frac{B}{L}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

MEDICATION RECORD

STUDY: ORAL PYRIDOSTIGMINE

Study Day	Date ddmmyy	Start drug administration (0-2400)	End drug administration (0-2400)	Route	Bottle I.D. #
5	13 Feb 86	0903	0903	PO	NA

DOSAGE (total) 16mg.**PHYSIOLOGIC VARIABLES**

Sample No.	Scheduled Time (hours)	Date ddmmyy	Scheduled Clock Time (0-2400)	Actual Clock Time (0-2400)	Pulse Rate bpm	Hand Grip L/R	Coord Test
	0	13 Feb 86	0847	0847	#80	#ND	#ok
	0.25	"	0918	0918	#80		-
	0.50	"	0933	0933	#84	#ND	#ok
	0.75	"	0948	0948	#80		
	1.0	"	1003	1003	#76	#ND	
	1.33	"	1023	1023	#76		
	1.66	"	1043	1043	#80		
	2.00	"	1103	1103	#80	#ND	
	2.5	"	1133	1133			
	3.0	"	1203	1203	#80		
	3.5	"	1233	1233			
	4.0	"	1303	1303	#ND	#ND	
	5.0	"	1403	1403			
	6.0	"	1503	1503	#ND	#ND	
	7.0	"	1603	1603			
	8.0	"	1703	1703			
	10.0	"	1903	1903			

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R M B</u> <u>F M L</u>	<u>024</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

CHEMISTRY VALUES
Laboratory

Johns Hopkins Hospital

	Screen	Predrug	Study		
TEST: NORMAL	03 Feb 86 ddmmmyy	11 Feb 86 ddmmmyy	11 Feb 86 ddmmmyy	14 Feb 86 ddmmmyy	Date
NA: 135-148 MEQ/L	142		141	144	
K: 3.5-5.0 MEQ/L	4.1		4.3	4.7	
CL: 96-109 MEQ/L	107		105	104	
CO2: 24-30 MEQ/L	24		24	29	
SUN: 12-25 MG/DL	11		16	10	
CREAT: 0.4-1.5 MG/DL	1.0		0.8	1.1	
GLU: 70-115 MG/DL	61		77	96	
T. BILI: 0.3-1.2 MG/DL	N.D.		0.5	0.4	
D. BILI: 0.1-0.4 MG/DL	N.D.		0.0	0.0	
CA: 9.0-11.0 MG/DL	N.D.		9.6	9.9	
PO4: 3.0-4.5 MG/DL	N.D.		4.2	3.6	
URIC A: 4.2-8.8 MG/DL	N.D.		5.5	5.6	
T. PROT: 6.0-8.5 G/DL	N.D.		7.2	7.7	
ALB.: 3.2-5.3 G/DL	N.D.		4.7	4.9	
AST: 0-35 IU/L	15		12	15	
ALT: 0-30 IU/L	10		12	11	
ALK PHOS: 0-95 IU/L	35		35	37	
CHOL: 151-268 MG/DL	N.D.		150	141	
LDH: 0-200 IU/L	N.D.		120	103	
CPK: 0-160 U/L (male)	N.D.	✓	77	70	

N.B.: CPK + LDH not done on days of drug dosing

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{P}{F} \frac{M}{M} \frac{B}{L}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

HEMATOLOGY VALUES

Laboratory

Johns Hopkins Hospital

Screen Predrug

Study

TEST	NORMAL	03 Feb 86 ddmmmyy	N.D. ddmmmyy	11 Feb 86 ddmmmyy	14 Feb 86 ddmmmyy	----- ddmmmyy	Date
Hgb	13.9-16.3	13.7		14.1	14.5		
PCV	41.0-53.0	41.5		42.2	43.3		
Plt	150-350	250		201	193		
RBC	4.50-5.90	5.03		5.18	5.28		
WBC	4500-11000	6100		6100	9100		
Bands	2-6%	9		2	6		
Polys	31-76%	64		48	66		
Eos	1-4%	0		4	3		
Bas		0		1	1		
Lymphs	24-44%	27		36	14		
Atyp Lym		0		1	2		
Monos	2-11%	0		8	8		
Other		0		0	0		
Retics	0.5-1.5%	ND	✓	0.8	0.8		

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	$\frac{R}{F} \frac{MB}{ML}$	024	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

URINALYSIS VALUES

Laboratory

*University of Maryland
Johns Hopkins Hospital
Clinical Pharmacology*

Screen Predrug

Study

TEST	NORMAL	06 Feb 86 ddmmmyy	N.D. ddmmmyy	11 Feb 86 ddmmmyy	14 Feb 86 ddmmmyy	_____ Date ddmmmyy
Color/Sp		yellow		N.D.	yellow	
Sp. Gr.		1.018			1.008	
pH		6.0			6.0	
Protein		(trace) neg			neg	
Ketones		neg			neg	
Occ Bld		neg			neg	
Bili.		neg			neg	
RBC		0			0	
WBC		0			0	
Casts		0			0	
Epi. Cel		0			0	
Crystals		0			0	
Bacteria		0			0	

ELECTROCARDIOGRAM

Date ddmmmyy	NORMAL check	ABNORMAL check	Describe abnormalities
06 Feb 86	✓		
11 Feb 86	✓		
14 Feb 86	✗ dp	✓	left atrial abnormality, questionable lead placement

INVESTIGATOR'S NAME	PT INITIAL	PT #	COMPOUND <u>Pyridostigmine</u>
Lietman	<u>R</u> F <u>M</u> M <u>L</u>	<u>024</u>	PROTOCOL <u>DAMD 17-85-C-5133-02</u>

ADVERSE EXPERIENCES

check if none occurred



ADVERSE EVENT		ONSET (Date/Time)	CESSATION Date/Time	SEVERITY (Check)	REL'N TO TEST DRUG	ACTION (Check)
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	
#		_____ dd mmm yy	_____ dd mmm yy	<input type="checkbox"/> Mild	<input type="checkbox"/> DEF.	<input type="checkbox"/> None
		_____ (0-2400)	_____ (0-2400)	<input type="checkbox"/> Mod	<input type="checkbox"/> PROB.	<input type="checkbox"/> Treatment
				<input type="checkbox"/> Sev	<input type="checkbox"/> POSS.	<input type="checkbox"/> Stop test drug
					<input type="checkbox"/> DEF. NOT	
					<input type="checkbox"/> UNKNOWN	

COMMENTS (Indicate # and event)